

Female reproductive system

Functions of ovaries

2 Functions :

1 Endocrinal

Estrogens & Progesterone.

2 Oogenesis

It occurs in intrauterine life.

●

Fetal life

1 Primordial

germ cells
in hind gut
migrate to
gonadal ridge

2 Primordial

ova (oogonia)
migrate to
ovarian cortex
& proliferate

6-7th W 10,000

8th W 600,000

3 Primordial

collect ovarian stroma
form granulosa cells

Follicles

11-12th weeks

20 W 6-7 million

at birth 2-2.5 million

4 {First} meiotic division at 5th month of gestation
crossing over of genetic material

●

Childhood

No pituitary gonadotropins Ovaries inactive

++ size of follicles & granulosa cells → Stratum granulosum

●

Puberty & adult life

300,000
- 400,000 Follicles

Prim oocyte
in primordial follicle
Diploid $2N$

2nd stage of 1st meiotic divis.

Before ovulation

FSH

Second oocyte

Haploid N

+ 1st polar body

{Second} meiotic division

Secondary oocyte

2-3 hours

After fertilization

LH

Maturing ovum

+ 2nd polar body
extra genetic material

N.B During reproductive period, only 450 follicles expel their ova
Arrest of 1st meiotic division in metaphase is due to:
Formation of ptn pp 39 mas in ovum
Fertilisation causes destruction within 30 min by:
Calpain (Ca^{++} dependent cysteine protease)

①

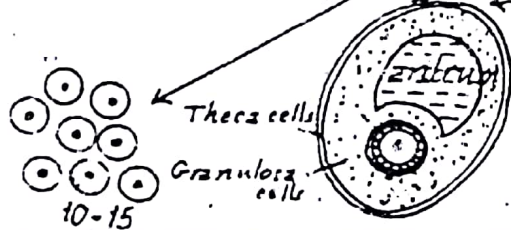
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● Ovarian cycle

28 days + 3 Days

4 phases



Follicular maturation

Graffian follicle

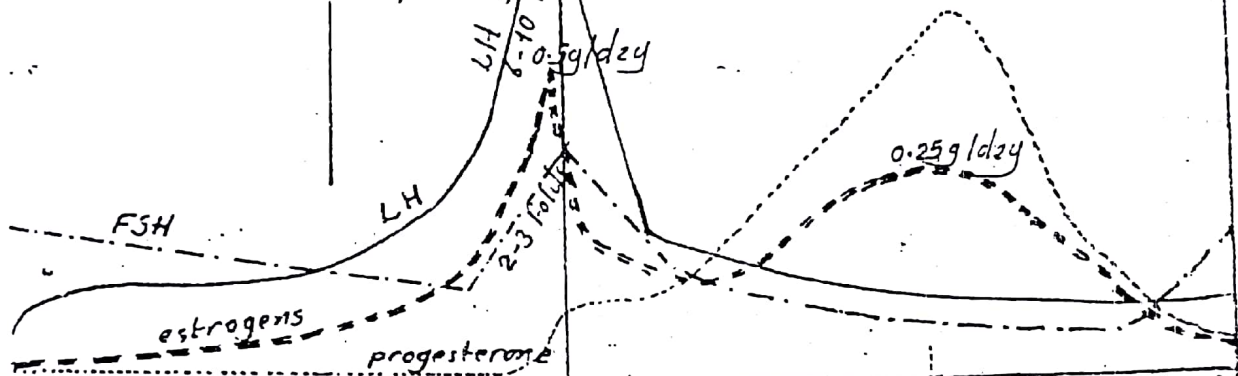
Ovulation

C. luteum formation

estrogens

estrogens & progesterone

FSH + LH = Folliculotropin.



Action of gonadotropins on Follicular cells

Cholesterol $\xrightarrow{\text{LH via cAMP}}$ Glandular THECA interna cells $\rightarrow$ Androgens (Testosterone androstenedione)

Androgen $\xrightarrow{\text{FSH via cAMP \& aromatase}}$ GRANULOSA cells $\rightarrow$ Estrogens

Estrogen $\rightarrow$ ++ NO of Granulosa cells $\rightarrow$ ++ Estrogen
High level of estrogen for a certain length of time (2 days)
 $\rightarrow$ midcycle LH surge & FSH surge.

Estrogen on granulosa cells $\rightarrow$ ++ FSH recep & recep sensitivity to FSH

Estrogen + FSH on granulosa cells $\rightarrow$ ++ LH receptors to respond to LH surge

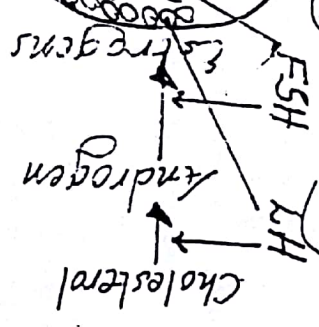
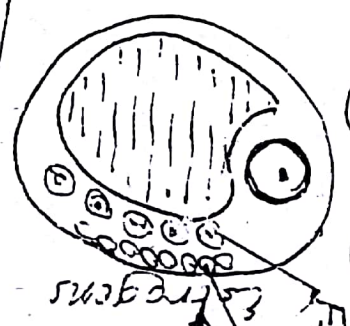
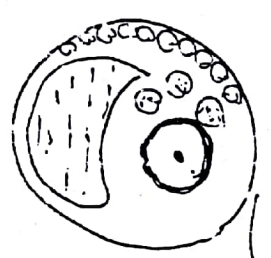
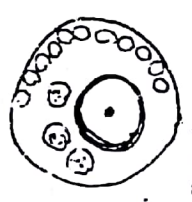
Estrogen + LH $\rightarrow$ ++ theca cells & their secretion

Follicles that don't develop LH receptors don't respond to LH surge & regress

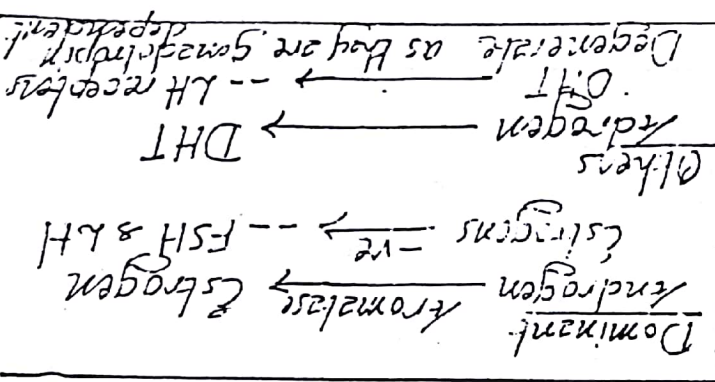
Ovarian cycle

Follicular maturation

- Ovary, controlled by FSH, LH, and estrogens/progesterone
- 4 phases
- Primary F
- Antral F
- Vesicular F



Grantham follicle



Ovulation

Cause
 LH surge (mainly) & FSH surge
 LH → ++ progesterone -- estrogen
 LH & Progesterone
 - Stroma is weak by proteolytic eng
 - Cavity P is ++ by PDS
 → rupture of follicle.

Luteal

LH → lutein cells → lipid, ER & bl vs
 Granulosa Theca
 Progesterone Estrogen inhibin
 FSH -- FSH & LH
 CL in 30 days
 CL -- HCG → 8W then replaced by placenta

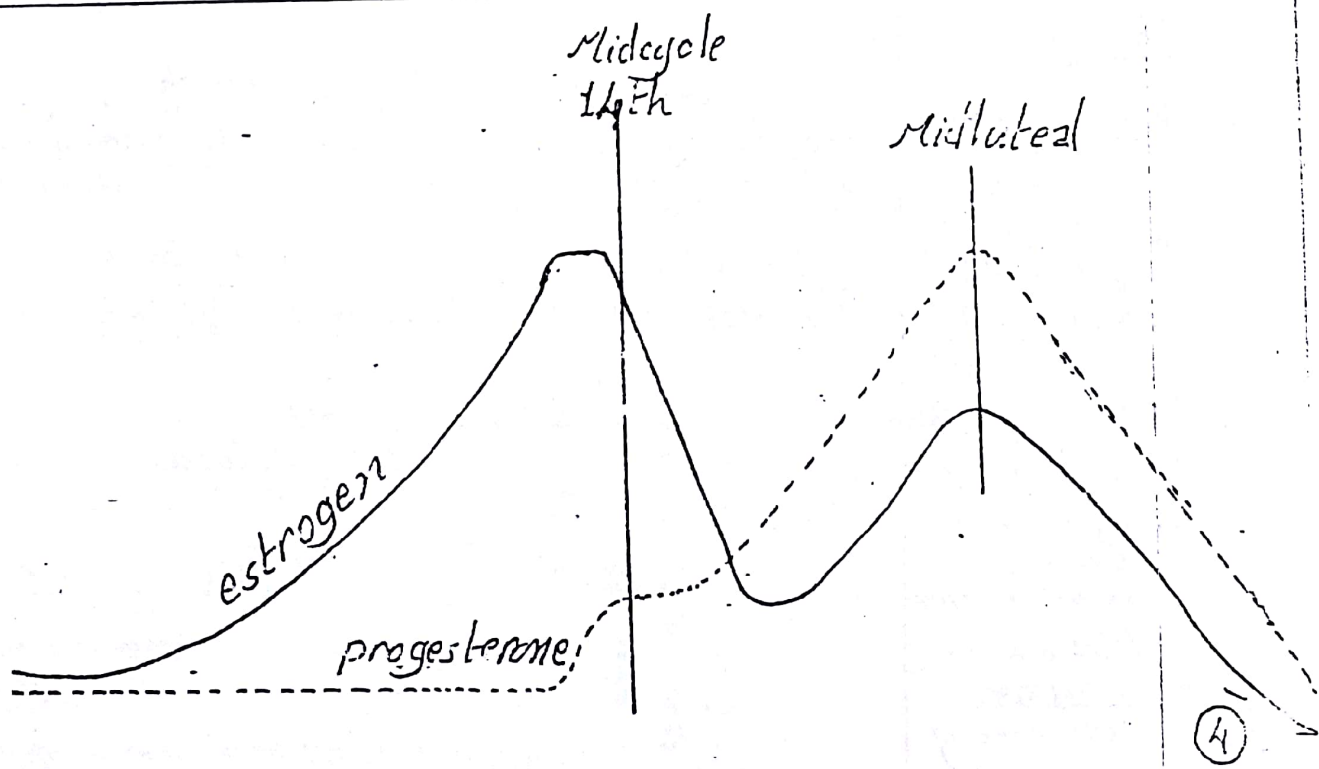
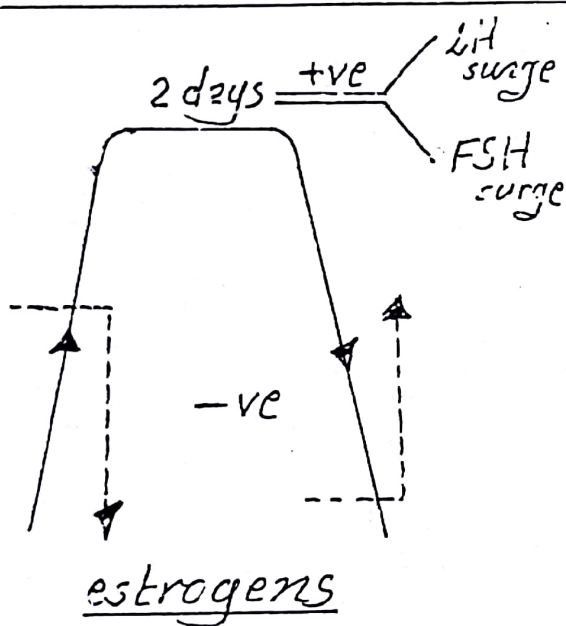
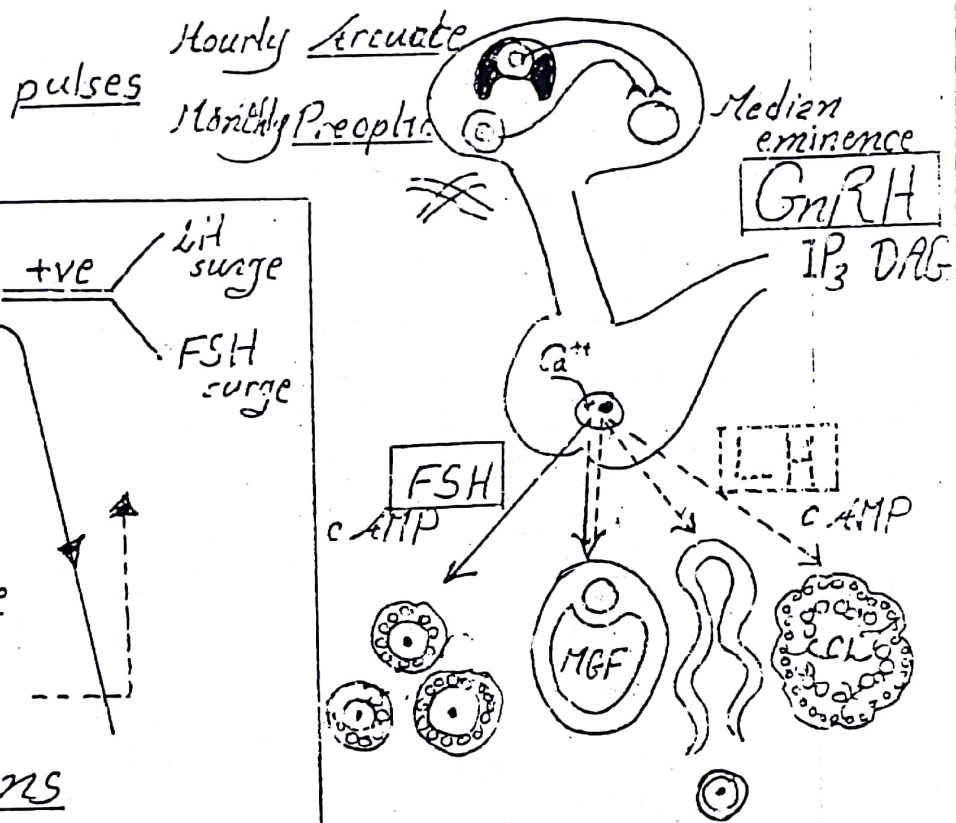
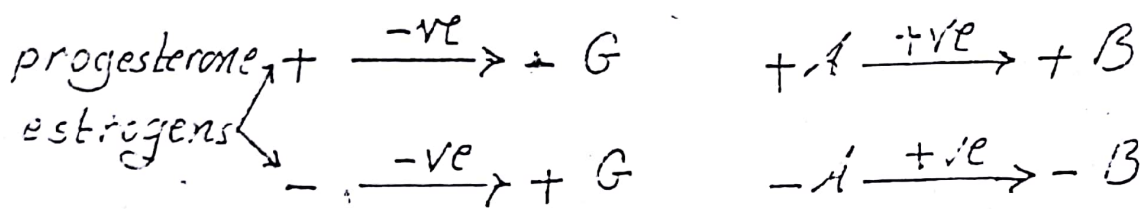
- Cholesterol → LH → Androgen → FSH → Estrogen
- Estrogen → Granulosa cells → FSH receptors → Estrogen
- Estrogen high level 2 days
- 2 surges LH 6-10 times 16 days before ovulation
- Estrogen + FSH → FSH 2-3 → LH receptors → Granulosa Theca cells

Ovarian cycle

- Site Ovaries
- Control FSH & LH
- Phases 4 (14b) day
- 1) ovulation release of mature ovum
- 2) production of ovarian hormones
- 3) oocyte from ruptured G. follicle

1 Follicular maturation	2 Full maturation of Graafian follicle	3 Ovulation	4 Luteal phase
<u>Control</u> mainly FSH, little LH <u>Changes</u> 10-15 follicles 1 Enlargement of ovum 2-3 folds 2 Prolif. of granulosa cells 3 Primary follicles: " " secrete zona pellucida (glycoprotein) 4 Preantral follicles surrounded by theca cells 2 layers 5 Granulosa (secreting) theca interna & theca externa 6 Granulosa cells develop gap junction for nutrients and FSH receptors. Theca cells develop LH receptors FSH & LH → ++ follicles size 4 Antral follicles large cavity filled with fluid 5 Vesicular follicles ovum & surrounding granulosa cells move to one pole & form cumulus oophorus. N.B. action of FSH & LH on follicular cells page 12	After a week, one follicle is chosen by programmed cell death. 1 Dominant (Graafian) follicle has FSH recept. leading to: ++ estrogen (granulosa cells) +ve → ++ FSH recept. action → ++ estrogen 2 Other (rest of) follicles Androgen & androstens + LH receptors → estrogen formation from androgen. Estrogen from dominant follicle → -- FSH & -- LH atrophy of other follicles (Gonadotropin dependent).	Midcycle LH surge main cause LH 16 H before ovul. ++ 6-10 folds FSH surge (mid cycle) ++ 2-3 folds → ++ progesterone 8 -- estrogen LH surge & progesterone 1 ++ proteolytic enzymes at stigma → weak 2 ++ local PGs (E & F) 3 a. new blood vessels b. VD → ++ fluid transud. → swelling → rupture of follicle → release of ovum with corona radiata. N.B. FSH (mainly) & LH plasmaogen in follicular fluid → plasmin dissolves bl. clot.	Granulosa & LH mainly lutein theca cells luteinization cells Lutein cells contain - Lipid - E. reticulum (excessive) - bl. vessels (rich) Corpus luteum secretes 1 Progesterone (primarily) From granulosa lutein cells reaches a peak in 7 days actions - Locally -- follicular growth - It down regulates estrogen recept 2 Inhibin 3 Estradiol From theca lutein cells action It is needed for progester. induced changes in endometrium involution of C. luteum → C. albicans After 10-14 days of ovulation or 2-3 months of pregnancy (cause) ++ progesterone & estradiol 2) ++ inhibin → -- FSH & LH N.B. new cycle -- progesterone estradiol inhibin → ++ FSH & LH

● <u>Uterine cycle</u> <i>menstrual cycle</i> <i>Endometrial cycle</i>	
Pre ovulatory phase	Post ovulatory phase
Degenerative Menstruation	Secretory (luteal) Pregestational phase
● <u>Duration</u> : 3-5	14th day 28 days
● <u>Control</u> : 0 Sudden withdrawal of estrogen ↓ progesterone	1 <u>Estrogen</u>
● <u>Changes</u> : ■ <u>Vasospasm</u> Duct to PGs ischemia necrosis ■ <u>Vasodil (PGs)</u> → Shedding 70-100 cc Disch. • unclotted bl. 75% arterial bl. • necrotic endom. Functional layer • cervical mucous • vaginal epith. • bacteria • unfertilized ovum • PGs & WBCs ■ <u>Vasospasm</u> stops bleeding	2 <u>Estrogen and Progesterone</u>
<u>Endometrial stroma & epith.</u> <u>Proliferation</u> 3-4 mm thick at ovul <u>Endometrial gland</u> <u>Proliferation</u> <u>Minimal secretion</u> <u>Blood vessels (spiral)</u> <u>Proliferate</u> Rich in Igs & WBC <u>Note</u> →	Lipid and glycogen deposit 5-6 mm thick at 28th D ++ <u>tortuosity (coiling)</u> Filled with <u>SECRETION</u> More <u>tortuous</u> ie corkscrew
Superf. (functional) layer	Deep (basal) layer
Outer 2/3 Implant blastocyst Proliferates shed off Supply Spiral tortuous arteries	Inner 1/3 Regenerate endom. Doesn't shed off (4)



Regulation of ovarian cycle

1) Gonadotropin releasing hormone GnRH

- Synthesis Hypoth. (Arcuate n. & preoptic area)
- Storage N. terminals project to median eminence
- Release Rhythmic pulses (oscillations)

- Arcuate nucleus Hourly rhythm i.e./Hour
→ upregulate GnRH receptor on ant. pit.
- Preoptic area Monthly rhythm i.e./M
→ GnRH surge → LH surge

Note $\frac{1}{2}$ life of GnRH in blood 2-4 min.

- Chemistry Decapeptide
Frequency of pulses ++ by catechol. 3-- by enkephalins & endorphins

- Mode of action nongenomic via G protein activate phospholipase C
- IP_3 ++ Ca^{++} (From ER lumen & influx of ECF)
→ exocytosis & release of gonadotropins

- DAG stim protein kinase C → ++ transcription & synthesis of

- Control (regulation) of GnRH 5

- 1 -ve feed back of ovarian steroids on hypoth & ant. pit.

- Estrogen at both low & high conc.

- Progesterone only at high conc.

Indirect i.e. via inhibitory interneurone in hypoth
In arcuate n. via opiates & in preoptic area via GABA

- 2 -ve feed back by inhibin

- Ant. pituitary : -- FSH (α and β) by -- mRNA

- Ovary : -- androgen → -- estrogen

- 3 +ve feed back by ovarian steroids

High level of estradiol for 2 days → midcycle LH surge
& to a lesser extent FSH surge via:

- Hypoth induces monthly GnRH surge in preoptic area

- Ant. pit sensitizes gonadotrophs to GnRH pulses.

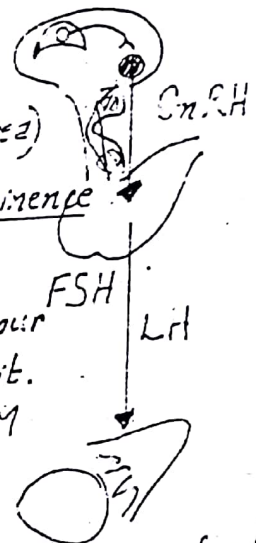
Less ++ in progesterone only augments LH surge.

- 4 +ve feed back by activin

- Ant pituitary : ++ FSH (β -subunit) by ++ mRNA

- Ovary : ++ estrogen

(5)



5) Psychic Factors

Stress & Suckling (lactation) Suppress GnRH release

B) Anterior pituitary FSH & LH

- Chemistry Glycoproteins

- Mode of action via c AMP on ovarian cells.

- Actions of FSH:

a early maturation of ovarian follicles

b Androgen $\xrightarrow{\text{Aromatase}}$ Estrogen
Theca cells Granulosa cells

c ++ estrogen formation by Granulosa cells

- Actions of LH:

a LH & FSH Graafian Follicle.

b Ovulation (LH surge) & C luteum formation.

c ++ androgen from glandular theca interna cells

d ++ estrogen & progesterone (main) from C. luteum.

e LH & FSH $\rightarrow$ growth of new follicles $\rightarrow$ new cycle

Hypothalamic - pituitary - ovarian hormone relation

Phase	Ovaries	Ant. pit & hypoth.
1 <u>Follicular growth</u>	-- estrogen & progest. $\xrightarrow{-ve}$ (due to Degeneration of C. luteum) ++ estrogen (granulosa cells) $\xrightarrow{-ve}$	++ FSH (2-3 folds) & ++ LH (2 folds) $\xrightarrow{-ve}$ -- FSH & LH (11th 12th day)
2 <u>Preovulatory & ovulation</u>	estrogen peak 13th day $\xrightarrow{+ve}$ ovulation & C. luteum formation. note progesterone only augments	preovulatory LH (main) & FSH surge $\xrightarrow{+ve}$ LH & FSH surge
3 <u>Postovulatory & menstruation</u>	C. luteum (stim. LH mainly) ++ estrogen, progest. inhibit Degeneration of C luteum $\rightarrow$ -- estrogen & progest. $\rightarrow$ menstruation.	$\xrightarrow{-ve}$ -- FSH & -- LH lowest level 2 to 3 days before menstruation (6)

Estrogens

C₁₈ steroids

- Types: Estradiol, Estrone & Estriol
 most potent least potent
- Secretion: Cholesterol $\xrightarrow{\text{LH}}$ Androgen $\xrightarrow{\text{FSH}}$ Estradiol
 Theca cells (Androstenedione) $\xrightarrow{\text{Aromatase}}$ Granulosa cells
- Sources: Ovary 2 peaks

Preculatory	Midluteal
just before ovul.	Mid luteal
Graffian follicle	C. luteum
Granulosa & theca cells	Lutein cells
380 µg/dL	250 µg/dL smaller longer

 Placenta
 Adrenal cortex
- Transport: Free 2% v.3 estradiol production in men 50 µg/dL
 Bound 98% Albumin 60% Globulins 38%
- Metabolism: Liver
 - oxidised or conjugated
 - Estradiol $\longrightarrow$ Estriol & estrone.

- Mechanism of action: • Genomic (++ DNA & ++ mRNA)
 • Non genomic $\longrightarrow$ -- FSH & LH via mem R

Actions

- 1 Embryonic life $\leftarrow$ ♀ Full develop. of uterus & vagina.
 $\leftarrow$ ♂ masculine ♂ brain $\longrightarrow$ ♂ sex behavior
- 2 Prepuberal -- GnRH due to hypoth. hypersensitivity
- 3 Non-pregnant adult

A Target organs

B General metabolism

- 1 Ptn anabolism: Bones & Genitalia
- 2 Maturation of ossific centres, ++ osteoblastic activity & union of epiphysis i.e Growth spurt.
- 3 Anti insulin
- 4 -- cholesterol & VD by nitric oxide.
- 5 (-- myocardial infarction inc) Salt & H₂O retention $\longrightarrow$ premenstrual dysphoria

C Endocrinal glands

- 1 ++ size of pituitary gland.
- 2 Regulation of gonadotropins - Discuss
- 3 ++ angiotensinogen, TBG & CBG

note estrogen receptors $\leftarrow$ Alpha: Hypoth, pit, uterus, Kidney & adrenal, testis & epididymis
 Beta: Bladder, Brain, Bone, prostate & pulm (lungs)

Actions of estrogen on target organs

1. Primary sex organ

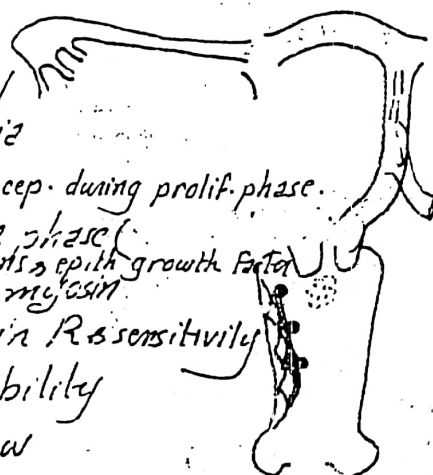
- Growth of ovarian follicles
- LH surge $\rightarrow$ ovulation & CL formation

2. Secondary sex organs

- Fallopian tube ++ motility
++ activity & NO of cilia
- Uterus max NO of estrogen Recep. during prolif. phase.

- endometrium Proliferative phase
via ++ growth factors (somatomedins & epith growth factor)

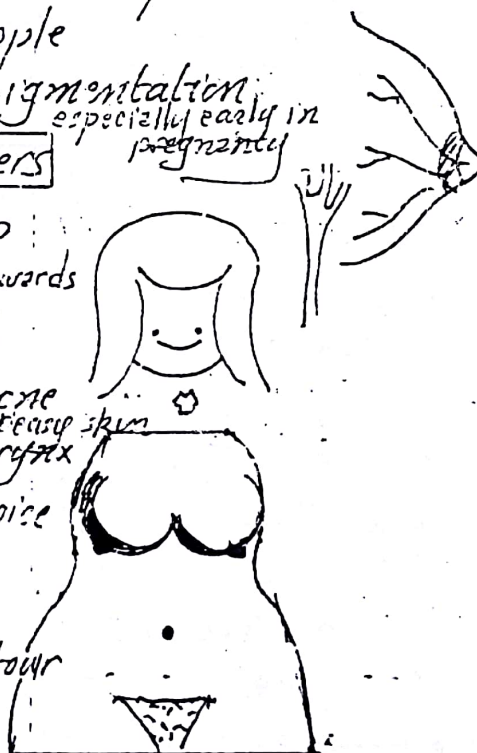
- myometrium ++ actin & myosin
++ oxytocin R sensitivity
++ excitability
++ bl. flow



- Cervix thin alkaline mucous (thinnest at ovulation)
Stretched into long threads (Spinnbarkeit - test)
Fern like pattern when dry.
- Vagina Stratification & keratinization
Glycogen $\rightarrow$ lactic acid (kill bacteria)
- Breast Enlargement & fat deposition & ++ bl. flow
Duct & nipple
Areolae: pigmentation especially early in pregnancy

3. Secondary sex characters

- Hair -- body ++ scalp
pubic ∇ base upwards
- Skin soft & smooth
sebaceous g. -- zone
excess $\rightarrow$ dry skin -- greasy skin
- Voice no effect on larynx
i.e. high pitched child voice
- Body narrow shoulder
broad pelvic
fat rounded contour
- Behavioural libido



note pubic & axillary hair growth by adrenal androgen.
make up of ♀

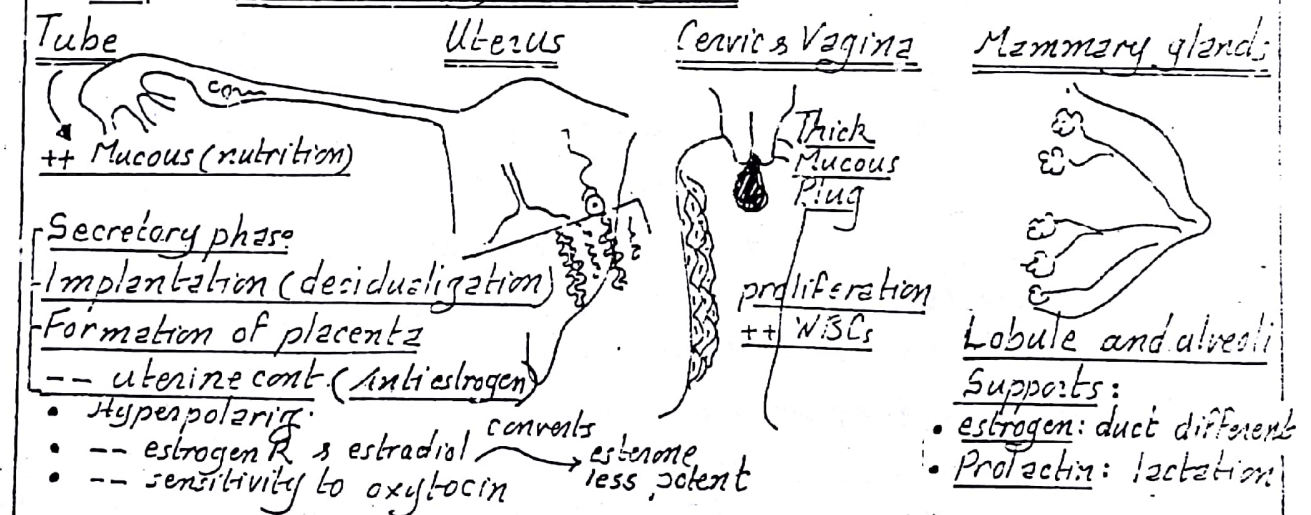
Progesterone

C₂₁ ovarian steroid.

- Sources Corpus luteum and placenta
small amount from ovarian follicles & adrenal cortex
Important intermediate in ALL tissues secreting steroid hormones
In C luteum, granulosa cells secrete progesterone by themselves
or theca cells provide pregnanolone.
- Plasma level in follicular phase 0.9 ng/ml
++ 20 time to one peak Midluteal 18 ng/ml 
- Transport Free 2%
Bound 98% (Albumin 80% Globulins 18%)
- Metabolism Liver converted to → pregnandiol & excreted in urine.
- Mechanism of action. Genomic
Progesterone releases its receptor from heat shock pt (++ Heat stress)
→ exposure of DNA binding domain of receptors (A & B)

- Actions 2 + 2 + 1

A On secondary sex organs:



B On prim sex organ: < minute amount augments LH surge Large amount -- LH → -- ovulation

C On respiration: stim resp → -- PCO₂

D Thermogenic: ++ 0.5°C at ovulation & end 1/2 of cycle basal body temp

E Electrolyte balance:

- Prog. like glucocorticoids on DCT → Na & H₂O retention
- Prog. on large dose competes with aldosterone → Na & H₂O excretion

Abnormalities of ovarian functions

- 1 primary hypogonadism Ovaries : Congenital absence or diseases
- 2 secondary Hypoth or pit : diseases

<u>Prepuberal</u>	<u>Manifestations</u>	<u>Postpuberal</u>
1 prim. amenorrhoea & sterility	Ovaries	Second. amenorrhoea & sterility
2 remain infantile	Second. sex organs	regress
3 don't appear	Second. sex characters	regress
4 Tall (delayed epiphyseal fusion)	Bones & muscle	osteoporosis & wasting

Estrogen secreting ovarian tumours

- child precocious pseudo puberty
- after menopause granulosa cell tumour.

Abnormalities of ovarian cycle.

① Anovulatory cycles

Definition : Failure of ovulation.

Causes :

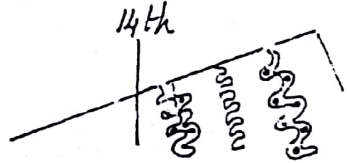
- Physiological 1st few cycles at puberty & last cycles at menopause
- Pathological
 - 1 Lack of sufficient LH surge
 - 2 Lack of ovarian response to LH
 - 3 ++ prolactin or stress $\rightarrow$ -- GnRH.

Characteristic : No C. luteum $\rightarrow$ no progesterone leading to

- Absence of secretory changes in endometrium
- Short cycles Mature Graafian follicle regresses with ovum inside.

Diagnosis of ovulation :

- 1 Endometrial biopsy : Secretory pattern
- 2 Folliculometry by sonar
- 3 Midcycle LH surge by blood hormonal assay
- 4 Rise of body temp 0.5°C in 2nd $\frac{1}{2}$ of cycle
- 5 ++ progesterone in plasma
- 6 Mittelschmerz pain i.e. lower abdom pain at ovulation due to peritoneal irritation



② Amenorrhoea

- a primary : associated with immature sexual signs. ⑩
e.g. small breast

b secondary stoppage of cycles after normal cycles.

- Causes
- 1 pregnancy main cause.
 - 2 emotional stress or systemic diseases.
 - 3 Hypoth., pituitary or ovarian diseases.
 - 4 Menopause.

- ③ Hypomenorrhea -- amount ④ Oligomenorrhea -- frequency
⑤ Metrorrhagia bleeding between periods ⑥ Dysmenorrhea Painful
⑦ Menorrhagia Abnormal profuse menstrual flow.

Menopause Stoppage of sexual cycles in ♀ (45-50 y)

- Cause Decreased number of ova (primordial follicle) → -- estrogen → no surge or inhibition of FSH, LH
- Hormonal changes X

Estrogen | -ve → ++ GnRH → ++ FSH
Progesterone | → ++ LH → ++ androgen
but no surge

- Manifestations

- 1 Secondary amenorrhea & sterility
 - 2 Second. sex organs & characters gradual regress
 - 3 Osteoporosis due to -- estrogen anabolic effect.
 - 4 Hot flashes 75% of women (Cause is unknown)
 - 5 Psychic disorders anxiety, irritability, depression & dyspnea
- ttt
- 1 Small doses of estrogen
 - 2 Milk & vitamin D to avoid osteoporosis

N.B No ♂ → menopause, despine -- testosterone in old age

Contraception Temporary prevention of pregnancy

- 1 Natural family planning (fertility awareness 30-90% success)
 - a Symptothermal method midcycle pain, ++ temp & thin cervical mucus.
 - b Safe period (rhythm method) no intercourse 3 days before & 3 days after ovulat.
1st Fertile day = Shortest cycle - 18 or longest cycle - 11 days
- 2 Hormonal suppression of ovulation (contraceptive pills)
 - a Single hormone therapy
 - 1 Estrogen pills daily for 3 Week/month -- GnRH inhibits ovulat.

Side effect bleeding (abdom), nausea or cancer (vaginal or cervical).

2 Synthetic progesterone pills progestin

Actions Thick cervical mucous & Atypical secreting endometrium.

It is: effective for 5 years

b Combined hormone therapy Progestins + estrogens 3W/M.

Actions -- LH (no ovulation) Tube alter motility (no fertilization)

Endometrium atypical Cervical mucous -- sperm migration

3 Intra-uterine devices (IUD) Plastic, metal & some release progestins

Actions Spermicidal & prevents implantation of fertilized ova.

4 Local devices progestin releasing → thick cervical mucous

a ♀ vaginal gellies or creams : spermicidal effect.

b ♂ condoms also prevent sexually transmitted diseases

5 Surgical tubal ligation.

6 Subcutaneous implants of progestin e.g. levonorgestrel

It will prevent pregnancy for 5 years

Fertilization

Fusion of sperm with mature ovum

- Time 14th - 16th day of ovarian cycle

- Site Ampulla of Fallopian tube.

- Preparatory steps for fertilization

1 2nd meiotic division begun & arrested in metaphase.

2 Ovum & corona radiata picked by fimbriae of F. tube.

- Ovum retains capacity for fertilization 12-14 hours

- Sperm " " " " 1-2 days

3 Ascent of spermatozoa to ampulla takes 1 hour

Aided by a alkaline seminal fluid -- vaginal acidity

b Vagina: semen coagulates

c Cervix thin secretion by estrogen

d Uterus & F tube cont → -ve p



a Only 50-100 sperm reach ovum

Fertilization involves :

1 Chemoattraction of sperm by ovum substance

2 Adherence of sperm to ZP₃ receptors

mediated by fertilin (ptn on surface of sperm head)

→ Acrosomal reaction (discuss)

3 Break down of fusion area with release of sperm nucleus into ovum cytoplasm

4 Fusion leads to

1 Prevention of polyspermy by

- -- membrane potential of ovum

- ++ IP₃ in oocytes → Ca release → exocytosis

of small granules → release of enzyme → hardening Zf

2 Completion of 2nd meiotic division

5 Formation of fertilization cone i.e. microvilli of ovum engulf sperm head in ovum cytoplasm.

Preimplantation

- 1 Zygote : mitotic division within ZP (zona pellucida)
 - 2 Zygote descends in F tube to uterus within 3-5 days
 - 3 Zygote → blastomere (2 cell stage) → morula (50-100 cells)
implantation in uterus takes 2-4 days
 - 4 Morula contains fluid filled cavity separating cells into:
 - Inner cell mass forms Embryonic tissue
 - Outer cell mass forms Trophoblast
 - 5 ZP shedding by lytic factor (plasmin) released from decidual cells
- N.B If cells divide into 2 separate group → identical twins
- 6 Pinopodes Finger like protrusion from endometrial cells approximate embryo & uterine epith close to each other

Implantation

- Time 6th - 8th days after ovulation.
- Three steps :
 - 1 Apposition of blastocyst with endometrial epith.
It occurs at site of rupture of ZP
 - 2 Adhesion of microvilli from trophoblasts to uterine epith. It involves ligand receptor (integrin family) → dislodging of uterine epith from basal lamina
 - 3 Invasion Trophoblast rapidly proliferates and differentiates into
 - inner cytotrophoblast
 - outer syncytiotrophoblastLong protrusions from syncytiotrophoblasts dissociate endometrial cells & penetrate basal lamina by secreting a Autocrine factor

b proteases c Tumor necrotic factor α
N.B For 8-12 W after implantation, embryo gets its
nutrients from digestion of decidua by trophoblasts

Continuation of pregnancy by prevention of regression
of CL via HCG of trophoblast

Corpus luteum remains 60 day, then placenta takes its role

Failure to reject fetal graft is due to

- 1 Expression of HLA-G by placental trophoblast instead of MHC class I, II
- 2 FAS - ligand on surface of placenta $\rightarrow$ apoptosis of T cells
- 3 -- circulating antibodies in the mother
- 4 Immunosuppressive agents e.g. HCG from blastocyst

Development of placenta

Placental barrier includes

- 1 Outer syncytial trophoblast
- 2 Middle mesenchymal layer
- 3 Inner cytotrophoblast
- 4 Wall of fetal capillaries

Placenta

Dia Thickness 3.5 mm Weight 500 g
Umbilical cord 2 fetal umbilical arteries & a vein which
connect fetal capillaries in choroid villi

Placental permeability

- Early months Low (small area & thick villi)
- Placenta gets older progressive ++ in permeability

- end of pregnancy -- permeability
Circulation of placenta

Exchange between fetal capillaries in chorionic (placental villi) & maternal sinuses branches of uterine arteries

Maternal blood flow Sluggish due to

- 1 Small blood lakes
- 2 Lateral spreading of bl. then reversal in direction to cascade over the villi
- 3 Geometry of maternal bl. vs in chorion plate
 - perpendicular spiral arteries
 - parallel venules
- 4 Uterine contractions interrupt venous drainage

Maternal placental fetal unit

Placenta can't form sex steroids (estrogen & progesterone)

- Mother supplies placenta by cholesterol & LDL
- Fetal adrenals & liver provides placenta with
 - 16 α hydroxylase for steroid formation
 - 17 α hydroxylase
 - 17, 20 desmolase for estrone & estradiol formation

Placental Functions :

① Diffusion of gases

- a Diff. of O_2 Maternal PO_2 50-60 mmHg, fetal PO_2 20-30 mmHg
Most of O_2 transported by fetal Hb is taken by tissues due to
- Fetal Hb has 20-30% more affinity to O_2

- Fetal Hb has 50% more conc. than maternal Hb.
- Bohr effect Fetal CO_2 -- O_2 affinity to maternal Hb.
- High COP relative to fetal weight.

b Diffusion of CO_2

PCO_2 in fetal blood is 3-5 mmHg higher than in maternal bl.
This is sufficient for CO_2 diff since solubility of $\text{CO}_2:\text{O}_2$ 20:1
 PCO_2 in maternal bl. is low due to resp. stim. by ++ progesterone.

② Diffusion of nutrients

a CHO glucose diffuses by facilitated diffusion.
placenta stores glycogen.

b Fat diffuses slower than glucose.

c Pln aa is transported by active transport.

d Minerals Na^+ , K^+ , Cl^- by simple diffusion.
 Ca^{++} , PO_4^{--} & Fe^{++} by active transport

e Vitamins 1 Fat soluble vitamins with fat.

2 H_2O soluble vit by simple diff except riboflavin & C by active transp.

③ Diffusion of fetal excretory product: e.g. urea & creatinine

④ Protective function of placenta: after 3 M

Impermeable

Toxins

Ig M

Bacteria

Permeable

Antitoxins

Ig G (Rh)

Virus & drugs $\rightarrow$ malformation

⑤ Endocrinal role of placenta

a HCG

Source Syncytial trophoblast.

Detected in bl. 6 days after conception

in urine 14 days after "

α unit = LH, FSH & TSH & β subunit.

Glycopln = Ltl but no -ve back with

progesterone & estrogen

- Reaches a peak 7-9 W of preg

Functions

1 Maintain Ch & pregnancy

b HCS

= human placental lactogen

= chorionic Glt prolactin

1 breast development

2 pln deposition

3 Provides glucose to

fetus viz:

++ FFA to mother

-- insulin sensit. to mother

- 2 On $\rightarrow$ fetal testes: testosterone 3Ds
 3 ++ growth of endometrium & storage of nutrients
 4 prevent fetal rejection
 5 helps implantation & placental formation

c Estrogens (estriol)
 syncytial trophoblast. Secreted by
 from dehydroandrosterone

- Functions
 1 growth of uterus
 2 growth of breast (ducts)
 3 relax. of pelvic ligaments
 4 ++ ox. globin recept on uterus

d Progesterone
 syncytial trophoblast

- 1 Decidual cell: develop.
 2 -- uterine contraction
 3 Breast alveoli
 4 ++ secretion of $\leftarrow$ endometr. F. tube

e Other hormones:

1 Relaxin (polypeptide) also from CL, breast, uterus & prostatic.

- ♀
 1 Relaxation of pelvic ligaments
 2 Softening
 3 Inhibition of uterine contractility
 4 Role in breast development



- ♂
 1 maintains sperm motility
 Helps sperm penetration of ovum.
 2 CRH ++ ACTH & ++ DHEA in fetal adrenal gland $\rightarrow$ ++ estrogen
 3 Inhibin & GnRH
 4 Prolactin
 5 Free HCG α subunit ++ endometrial prolactin secretion

Other hormones secreted during pregnancy

- 1 Pituitary gland is stimulated by placental hormones
 ++ ACTH, TSH & prolactin & FSH & LH
 2 Pancreas ++ insulin.
 3 Parathyroid ++ PTH (maintains Ca^{++}).
 4 Thyroid ++ T_3 & T_4 .
 5 Adrenal cortex ++ glucoc & mineralocorticoids.

Pregnancy tests

Depend on detection of HCG in urine or blood.

- ① Agglutination (immunological) tests rapid & specific
 - a Urine + HCG antibodies + sensitised RBCs or latex coated by HCG
 - ♀ is pregnant : no agglutination of RBC or latex particle
 - ♀ is not ,, : agglutination occurs
 - b Direct agglutination (coagulation)
 Urine + Latex coated with anti HCG $\xrightarrow{\text{♀ pregnant}}$ coagulation
- ② Radioimmunoassay used for polypeptide β subunit recept. of HCG

Parturition = Labour = delivery = expulsion of fetus & placenta

It requires strong coordinated U. cont. aided by vol. abdom. ms contractions.

- ① Hormonal Factors ++ Uterine cont.
 - a ++ ratio of estrogen/progesterone $\rightarrow$ ++ uterine cont.
 At 7th M, progesterone $\pm$ or - & estrogen continues to ++
 (-- U. cont.) (++ U. cont.)
 - b Oxytocin (fetal & maternal) Direct & indirect viz FGN
 estrogen ++ synthesis & sensitivity of oxytocin receptors
 - c Fetal hypothalamic-pituitary adrenal axis ++ U. contraction
 - d Prostaglandins from decidua & fetal membranes.
 - Direct U. contraction - induce oxytocin actions
 - Softens, dilates & thins out the cervix.

② Mechanical Factors

- a Stretch of U. muscles $\rightarrow$ U. cont.
- b Stretch of cervix $\rightarrow$ U. cont.
- c +ve feed back theory of labour

- cervical stretch $\rightarrow$ U. cont. $\rightarrow$ more cervical stretch.
- cervical stretch $\rightarrow$ Oxytocin $\rightarrow$ more cervical stretch.

Stages of labour 1st U. cont. till fully dilated cervix. (Ferguson reflex)

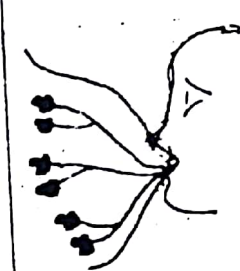
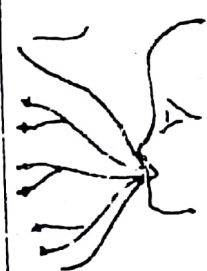
2nd expulsion of baby from birth canal.

3rd expulsion of fetal membranes & placenta



Lactation

Breast development starts at puberty & is completed during pregnancy (glandular tissue)

<u>Growth</u>		<u>Secretion</u>	
<u>Duct system</u> ++ stroma ++ fat deposition 	<u>Lobule alveoli</u> secreting charact. of alveolar cells 		<u>Milk secretion</u> (milk let down) via cont. of myoepith cells on outer alveolar wall. 
<u>ESTROGENS</u>	<u>PROGESTERONE</u>	<u>PROLACTIN</u> 5th W till birth Ant. pituitary	<u>OXYTOCIN</u> contacts myoepith cells Posterior pituitary
<u>Aided by</u> Prolactin & GH Insulin & Glucocorticoids		<u>SUCKLING</u> HCS 5th W provides fatty acids, glucose & Ca ⁺⁺	

Notes Colostrum 1st W after birth, contains more immunoglobulins & protein than milk.
 Milk 2nd & 3rd W, contains more lactose, fat & higher calories.
Initiation of lactation 5th M of gestation, small amount of milk.
 After labour, expulsion of placenta → -- estrogen & progesterone
 → removal of inhibitory effect of estrogen on prolactin
 Estrogen & prolactin synergize each other on breast growth not lactation.
Effect of lactation on menstrual cycles Prolactin → -- GnRH
 → no ovulation & -- estrogen & progesterone. May amenorrhea for 25-30 W.
 50% of cycles in 1st 6 M anovulatory

Chiari-Frömmel Syndrome

= Persistence of lactation & amenorrhea in unnursing ♀ after delivery.
Cause → Prolactin secretion without FSH & LH secretion
 NB Nonpregnant ♀ having galactorrhea & amenorrhea with high prolactin level is due to pit. tumour or injury of pit. stalk.

Good Luck



(20)

Female reproductive system

Functions of ovaries:

- 1- Oogenesis; formation of ova.
- 2- Hormonal functions; secretion of estrogen & progesterone.

OOGENESIS

In contrast to spermatogenesis, oogenesis occurs in intrauterine life.

A) During foetal life:

1- Primordial germ cells migrate from the hind gut to the gonadal ridge.

Primordial germ cells differentiate into primordial ova (oogonia)

2- Primordial oogonia migrate & proliferate in the fetal ovarian cortex by mitotic division.

By 6- 7 weeks' intrauterine life, 10 000 oogonia are present.

By 8 weeks, they reach a total of 600 000

The medulla of the gonad regresses, while the cortex greatly increases in thickness.

Masses of the cortical cells then split on the inner cortical surface & surround one or several primordial germ cells.

3- Primordial follicle:

At 11- 12 weeks, each oogonia collects a layer of spindle shaped cells from the ovarian stroma around it.

These cells change to granulosa cells & form primordial follicle.

Follicles number:

a) At 20 weeks of gestation, 6- 7 million

b) At birth 2- 2.5 millions

c) At puberty, 300 000- 400 000

Notes:

- From 13- 50 years of age, only 450 of these follicles develop enough to expel their ova, one each month, the remainder degenerate

4- The 1st stage of meiotic division of primordial follicle occurs at 5th month of gestation

During the prophase of 1st meiosis, when the cells contain duplicated set of 23 chromosomes, crossing over of the genetic material occurs.

Meiosis, then becomes arrested by inhibitory factors from the granulosa cells surrounding the oocytes (diplotene stage)

Note: These development changes depend on placental gonadotrophin. So, ovaries remain inactive from birth to puberty.

B) DURING CHILDHOOD:

Ovaries are inactive (no pituitary gonadotrophins).

Follicles increase in size due to +++ mRNA.

Granulosa cells proliferate to form stratum granulosum.

C) DURING PUBERTY & ADULT LIFE

At puberty, the remaining primordial follicles are 400,000.

The primary oocyte (containing diploid number of chromosomes) enters the **second stage of first meiotic division** (metaphase) under the effect of FSH shortly before ovulation to give rise to secondary oocyte (haploid number of chromosomes) & first polar body.

Secondary oocyte starts **2nd meiotic division**, which is not completed until fertilization to release 2nd polar body.

These polar bodies (1st & 2nd) are then discarded outside the oocytes to degenerate eventually.

Thus 23 unpaired chromosomes remain in the secondary oocytes.

OVARIAN CYCLE

- It occurs in the ovaries.
- It is under the control of pituitary gonadotrophins (FSH & LH).
- **Aim:** ovulation & release of ovarian hormone, which controls menstrual cycle.
- **It is composed of 4 phases:**

1) FOLLICULAR MATURATION:

Control: mainly FSH & small doses of LH.

Changes:

- 1- Moderate **enlargement** of ovum 2 – 3 folds.
- 2- Proliferation of **granulosa cells**.
- 3- Granulosa cells secrete glycoprotein called **zona pellucida**. The follicle is now called the **primary follicle**.
- 4- The surrounding stroma cells form theca cells. The follicle is now called the **preantral follicle**.

Theca cells are divided into 2 layers:-

- a- Glandular theca interna secreting steroids like granulosa cells.
- b- Fibrous theca externa, highly vascular connective tissues.

Granulosa cells develop receptors for FSH.

Theca cells develop receptors for LH.

FSH & LH are necessary for growth of the follicle & to convert preantral follicle into large vesicular follicle, this takes place as follows:

- Proliferation of granulosa & theca cells → ++ in follicular size.

Gap junctions develop among granulosa cells as well as between the ovum & granulosa cells.

These junctions act as route of transport of nutrients & information.

- Formation of large cavity filled with follicular fluid & known as **antral follicles** then vesicular follicles.

The ovum & its surrounding granulosa cells are located at one pole of the follicle to form cumulus oophorus

Action of gonadotrophins on the follicle cells & the initial production of estrogens:

1- LH $\rightarrow$ ++ cAMP $\rightarrow$ ++ LDL receptors.

The theca interna cells start to produce androgens (androstendione & testosterone) from cholesterol.

Androgens diffuse to granulosa cells.

2- FSH $\rightarrow$ ++ cAMP that stimulates the granulosa cells to produce aromatase that converts androgen to estrogen.

Estrogens accumulate in the follicular fluid of the antrum & some passes to blood

3- Estrogens bind to their receptors in the granulosa cells to stimulate the production of more granulosa cells which in turn produces more estrogens

- When estrogen in blood reaches sufficiently high level for a certain length of time, it exerts a **positive feedback effect** on:

a) The pulsatile secretion of GnRH

b) The release of gonadotrophins from the sensitized anterior pituitary cells

a & b leads to the **midcycle LH surge**

- Estrogen increases the FSH receptors & the sensitivity of granulosa cells to FSH

- FSH & estrogen ++ LH receptors on the granulosa cells which enables the follicle to respond to LH surge.

Follicles that have not developed LH receptors are unable to respond to the LH surge & hence undergo atresia.

- The estrogens & LH secreted in increasing amounts cause marked proliferation of theca cells & their secretions.

2) FULL MATURATION OF ONE FOLLICLE: GRAFFIAN FOLLICLE

After a week of follicular growth, one of the follicles (10 – 15) begins to outgrow all the others, which begin to involute (atresia).

This programmed physiological cell death is caused by:

a- Higher number of FSH receptors in the dominant follicle leading to:

i- Higher rate of granulosa cell proliferation with subsequent increase in aromatase production

ii- Higher estrogen content, which acts on dominant follicle $\rightarrow$ ++ FSH receptors & ++ FSH action.

b- Higher vascularity in the dominant follicle.

c- Presence of 5 α reduced androgen in the remaining slow growing follicle, which inhibits:

i- LH receptor formation.

ii- Estrogen formation from androgen.

Result: ++ growth & size of the dominant follicle without further ++ in gonadotrophin to give Graffian follicle (1.5 – 2 cm).

3) OVULATION: IN 14TH DAY

Definition: it is the release of mature ovum (secondary oocyte) from a ruptured Graffian follicle into the peritoneal cavity.

Control: LH is essential for final follicular growth & ovulation.

2 days before ovulation, the LH secretion by the anterior pituitary is increased 6 – 10 fold & reach a peak 16 hours before ovulation i.e. LH surge.

FSH is also increased by 2- 3 folds. Both FSH & LH act synergistically to cause:

- very rapid growth of follicle & protrusion of stigma.
- --- estrogen secretion.
- Beginning of progesterone secretion in minute amount, which progressively increase.
- FSH & to lesser extent, LH stimulate the release of plasminogen activator from granulosa cells that converts plasminogen in follicular fluid to plasmin. Plasmin dissolves blood clots
- Just before ovulation, 1st meiotic division is completed with the formation of the secondary oocyte & 1st polar body, which is discarded.

Few hours before ovulation:

- Both LH & progesterone ++ activity of proteolytic enzymes e.g. collagenase within the follicle → degeneration of stigma → oozing of fluid from the follicle through it

- Local prostaglandins E & F cause:

- a) Vasodilatation, plasma transudation into the follicle
- b) Contraction of the smooth muscle of theca externa

- ~ - Rapid growth of new blood vessels into the follicular wall with local secretion of prostaglandins, which cause VD → plasma transudation into follicle → More swelling → rupture of follicle → release of ovum surrounded by layer of granulosa cells (corona radiata). Then, the fimbriated ends of the Fallopian tube pick the ovum.

After ovulation, the secondary oocyte begins the 2nd meiotic division, which is only completed after fertilization.

4) AFTER OVULATION: LUTEAL PHASE

The theca cells at the periphery of the follicle differentiate into stroma cells & theca lutein cells. The process is known as luteinization

They are characterized by:

- The presence of lipid inclusion.
- Extensive endoplasmic reticulum.
- Secretion of progesterone in addition to estrogen.
- Rich vascular supply.

The process of luteinization forms corpus luteum.

The corpus luteum lasts 10 – 14 days after ovulation.

- If pregnancy does **not** occur, it begins to involute by luteolysis & stops secretion and becomes fibrous tissue (**corpus albicans**) 4 days before the next ovarian cycle.
- If pregnancy occurs, it persists **2 – 4 months** under the effect of chorionic gonadotrophin of placenta.

Corpus luteum produces both:

- a) Estrogens mainly estradiol from theca lutein cells
- b) Progesterone from the granulosa lutein cells.

However, the luteal phase is primarily dominated by the progesterone secretion.

Progesterone levels rise sharply & peak in 7 days.

Progesterone may act:

- a) Locally to inhibit follicular growth during the luteal phase
- b) Centrally by inhibiting gonadotrophin secretion.

Progesterone has also anti-estrogen action. It down regulates the estrogen receptors, thus reducing the estradiol effectiveness & folliculogenesis.

Estradiol produced by corpus luteum is necessary for the occurrence of the progesterone- induced changes in the endometrium.

Causes of involution of corpus luteum:

- 1- Estrogen & progesterone of corpus luteum leads to --- FSH & LH.
- 2- Inhibin of corpus luteum leads to --- FSH mainly & LH.

Beginning of new ovarian cycle:

-- FSH & LH → --- estrogen, progesterone & inhibin. So, no -ve feed back leading to +++ FSH & LH which initiate the growth of new follicles (10-15).

MENSTRUAL (ENDOMETRIAL) CYCLE

Endometrium is divided into 2 layers:

Superficial (functional) layer	Deep basal layer
Outer 2/3	Inner 2/3
Implants the blastocyst	Regenerates endometrium.
Proliferates, secretes and then is shed off.	It does not shed off
Supplied by spiral tortuous arteries.	Supplied by short straight arteries.

PHASES OF MENSTRUAL CYCLE:

A) DEGENERATIVE PHASE (MENSTRUATION):

- Menstruation lasts 3-7 days.
- If fertilization of the ovum does not occur, the corpus luteum degenerates, resulting in marked decrease ovarian hormones; i.e. estrogens and progesterone (2 days before the end of the monthly ovarian cycle) leading to:

Vasospasm of the tortuous spiral endometrial arteries by locally secreted prostaglandins → Ischaemia and necrosis of the functional mucosal layer of the endometrium → Release of vasodilator substances from necrotic tissue (e.g. prostaglandins) together with vasospasm leads to seeping of blood under the necrotic functional layer, which is separated and expelled during menses from the uterine cavity, including the unfertilized ovum.

The prostaglandins are formed from phospholipids by the enzymes released from lysosomal membrane breakdown of necrotic endometrial cells.

Onset of menstruation:

- During normal menstruation, ^{75% arterial bl.} 70-100 ml of menstrual discharge is expelled, formed mainly of unclotted blood (due to fibrinolysin released from the necrotic endometrial tissue), desquamated endometrial and vaginal epithelial cells, cervical mucus, bacteria & prostaglandins.
- N.B. necrotic endometrial tissue releases also large numbers of leucocytes (leukorrhea) during menstruation. These leucocytes have a protective value in making the uterus highly resistant to infection.

Factors affecting the amount of menstrual blood flow:

- a) Thickness of endometrium
- b) The concomitant use of medications that dilate blood vessels or those that interfere with blood clotting
- c) Diseases affecting clotting mechanisms

B) PROLIFERATIVE (ESTROGEN) PHASE:

- It begins on the fifth day from the onset of menstruation and lasts up to 14th day i.e. it coincides with follicular phase of the ovarian cycle.
 - After menstruation, there is a thin layer of endometrium, which contains endometrial stroma, the deep portions of endometrial crypts & glands.
 - Under the influence of estrogen, the following events occur:
 - 1- Re-epithelization of endometrium (regeneration) due to rapid proliferation of the endometrial stromal and epithelial cells.
- By the time of ovulation, the endometrium is 3-4 mm thick.

2- Progressive growth of endometrial glands, but with minimal secretion.

3- Development of endometrial blood vessels. Blood in these vessels is rich in leucocytes and immunoglobulins.

C) SECRETORY (PROGESTATIONAL) PHASE:

It begins from the 14th day i.e. ovulation till the onset of the next menstruation.

- This phase is mainly dependent on progesterone, which is secreted in large quantities from corpus luteum under LH effect. Also estrogen causes slight additional proliferation of the endometrium.

- Progesterone has the following effects on the endometrium.

1- Marked increase in tortuosity (coiling) of endometrial glands, and increase in their secretion.

2- Highly tortuous dilated blood vessels.

3- Increased cytoplasm of the stromal cells with increased lipid and glycogen deposits.

The endometrium by the end of this phase reaches of 5-6 mm thickness.

N.B. proliferative and secretory phases produce a highly secretory endometrium, which can provide nutrition needed for the implanted fertilized ovum.

Regulation of the female ovarian cycle

A) Gonadotrophin releasing hormone (GnRH):

- Site of synthesis:

GnRH is formed in arcuate nucleus & preoptic area of the hypothalamus.

- Storage:

GnRH is stored in nerve terminals which project to the median eminence near the portal vessels.

- Release:

GnRH is released in rhythmic pulses (oscillations) into the portal vessels once per hour i.e. intermittently stimulating the gonadotrophins of anterior pituitary.

This hourly release of the gonadotrophins is the control key of cyclic gonadal & thus the reproductive function

Note:

1/2 life of GnRH in blood is 2- 4 minutes

Hourly pulses upregulate the gonadotrophins' GnRH receptors thus stimulating the release of gonadotrophins.

Arcuate nucleus causes the hourly rhythmic pulses of GnRH.

Preoptic area causes the monthly rhythm of GnRH surge that produces the LH surge

- Chemistry:

GnRH is decapeptide

- Mode of action:

GnRH binds to G protein- linked receptor on the surface of gonadotroph cell → activation of phospholipase C (PLC) which hydrolyses PIP₂ to:
a) IP₃ that ++ release of Ca⁺⁺ from the endoplasmic reticulum & influx of extracellular Ca⁺⁺.

The elevated Ca⁺⁺ → exocytosis & release of gonadotrophins

b) DAG stimulates protein kinase C that indirectly leads to increase in gene transcription & synthesis of gonadotrophins

- Control & regulation of GnRH & gonadotrophins:

A) Negative feedback by ovarian steroids:

During the menstrual cycle, the ovarian estrogens & progesterone feedback negatively on both the hypothalamus & the anterior pituitary

The estrogens exert -ve feedback at both low & high concentrations.

Progesterone is effective at only high concentrations.

The -ve feedback of ovarian steroids on GnRH is indirect i.e. estrogens stimulate interneurons that inhibit GnRH neurons in the arcuate via opiates & preoptic area via GABA

Progesterone in the luteal phase stimulate inhibitory opioidergic interneurons in the hypothalamus that inhibit arcuate GnRH neurons.

B) Negative feedback by inhibins:

Inhibins inhibit FSH secretion by ----- mRNA levels for both alpha & beta subunits of FSH.

In addition, inhibins exert inhibitory intra- ovarian effect on androgen production thus decreasing estrogen formation.

C) Positive feedback by ovarian steroids:

At the end of the follicular phase, the rise of estrogen levels to a very high threshold for a minimum of 2 days has 2 effects:

- 1- Sensitizes the gonadotrophs in the anterior pituitary to GnRH pulses
- 2- Induces GnRH surge by GnRH neurons in the preoptic area

This causes the midcycle LH surge & to a lesser extent FSH.

The increasing but still low levels of progesterone produces positive feedback that only augments the effects of estradiol but it is not the primary trigger of LH surge.

D) Positive feedback by activins:

- 1- Activins ++ mRNA levels of beta subunit of FSH → FSH release
- 2- Direct ++ ovarian estrogen

E) Psychic factors:

- . Emotional stress decreases GnRH
- . Suckling & lactation that may inhibit GnRH secretion → lactating amenorrhea

B) ANTERIOR PITUITARY:

Secretes the gonadotropins FSH and LH.

- Glycoproteins secreted by basophilic Cells (gonadotropes).
- Act via cAMP 2ry messenger on the ovarian cells.

Function of Follicle - stimulating Hormone (FSH):

- a) Early maturation of ovarian follicle.
- b) Stimulates the conversion of androgens secreted by theca interna by aromatization to estrogens.
- c) Stimulates estrogen formation by granulosa cells.

Function of Luteinizing Hormone (LH):

- a) It helps FSH in the maturation of ovarian follicles into graafian follicles.
- b) It is responsible for ovulation and corpus luteum formation.
- c) It stimulates estrogens and progesterone secretion from corpus luteum.
- d) It stimulates androgen formation from theca interna.
- e) It stimulates (with FSH) the growth of new follicles to start a new monthly cycle.

**HYPOTHALAMIC - PITUITARY - OVARIAN
HORMONES RELATONSHIP**

(1) Follicular growth phase (preovulatory):

- The decreased amounts of estrogen and progesterone, due to degeneration of corpus luteum → ++ FSH and LH secretion due to release of the hypothalamus and the anterior pituitary gland from the negative feedback effect of the ovarian hormones.
- ++ FSH (2-3 folds) and LH (2-folds), initiate new follicular growth (of 10-15 follicles), with progressive increase in estrogen formation by granulosa cells.
- ++ Estrogen → -- rates of secretion of FSH & LH at 11th - 12th day.

(2) Preovulatory surge of LH and FSH:

- When estrogen reaches its peak secretion at 13th day, there is a sudden increase in the secretion of both FSH & LH leading to preovulatory surge of LH followed by ovulation.
- The result of ovulation is corpus luteum formation.

N.B. progesterone secretion from the ovarian follicle also may be a cause for LH and FSH surge.

(3) Postovulatory secretion of the ovarian hormones and depression of gonadotropins:

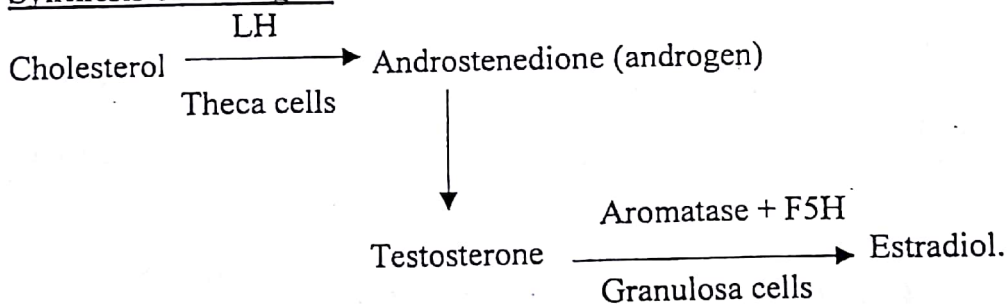
- Corpus Luteum secretes estrogens, progesterone and inhibin, mainly due to LH stimulation and to a lesser extent FSH.
- ++ Estrogen and progesterone → negative feed back effect on hypothalamus and anterior pituitary → -- FSH and LH to reach their lowest levels 3-4 days before menstruation.
- -- FSH and LH → degeneration of corpus luteum → -- estrogen, progesterone and inhibin → shedding of the uterine endometrium (menstruation).

OVARAN HORMONES

1- ESTROGENS:

The naturally occurring estrogens are estradiol (most potent), estrone, and estriol (least potent).

Synthesis of Estrogen:



Secretion of Estrogens:

- Estrogens are secreted by theca interna and granulosa cells of growing follicles, Graafian follicle, corpus luteum, placenta and adrenal cortex.
- N.B. the stromal cells of the ovary have the potential to form androgens & estrogens in minute amounts in normal pre-menopausal females.

- Estrogen secretion shows cyclic variation with two peaks:-

<u>Preovulatory peak</u>	<u>Midluteal peak</u>
Occurs just before ovulation	Occurs during the midluteal phase
Estrogen is secreted from theca interna and granulosa cells of mature graafian follicle.	Estrogen is secreted from corpus luteum.
The rate of secretion is maximal (380 µg/dL)	The secretory rate is smaller (250 µg/dL)

Transport and Metabolism of Estrogens:

- Plasma estradiol level at the follicular phase is 2% is free & 98 % bound form: [60% bound to albumin & 38 % bound to gonadal - binding globulin (GBG)].

- Estrogens are metabolized in the liver:

a) They are oxidized and converted to glucoronide and sulfate conjugates and excreted in urine mainly and some in bile.

b) Estradiol is converted to the least potent estriol and estrone.

There are 2 estrogen receptors (α and β).

Estrogen secreted in ovarian follicles act via estrogen β receptors.

Mechanism of Actions of estrogens (Steroid hormones) *A) Genomic B) Non genomic*

A) Estrogens unlike other steroids, combine with nuclear receptors in the target cells. This complex:

a) Interacts with steroid response element to produce mRNA resulting in protein synthesis

b) Increases DNA synthesis (mitogenic effect of estrogens)

estrogens combine with cytoplasmic receptors in the target cells. This complex binds to DNA $\longrightarrow$ mRNA formation $\longrightarrow$ ribosomal protein synthesis

$\longrightarrow$ Hormonal effects.

B) Non genomic (rapid) via mem receptors to produce feedback effect on FSH & LH

ACTIONS OF ESTROGENS: -

1) In the embryonic life: - Estrogen is essential for the full development of uterus and vagina.

In male embryos, testosterone converted to estrogen in the brain to masculine the male brain (male sex behavior)

2) Prepuberal effect of estrogen: - low estrogens level causes inhibition of GnRH secretion due to hypothalamic hypersensitivity.

Estrogen alpha receptors are located in hypothalamus, pituitary, uterus, kidney, adrenal gland, testis & epididymis.

Estrogen beta receptors are located in prostate, lungs, bladder, brain & bone

3) Effects of estrogen in the non-pregnant adult: -

A) On Primary Sex Organs:

1. Estrogens facilitate the growth of ovarian follicles.

2. Estrogens stimulate LH surge. Therefore, they essential for ovulation and corpus luteum formation.

B) On Secondary Sex Organs:

Estrogen is responsible for growth, development and maintenance of:

1. Uterus:

a) Endometrium:

Estrogens receptors are maximum during the proliferative stage & declines after ovulation in response to progesterone.

Estrogens effects on endometrium:

i- Stimulate proliferation, growth & maturation of the endometrium via:

1- Expression of certain genes

2- Inducing the synthesis of growth factors e.g. somatomedins & epidermal growth factor

ii- High development of stromal components of endometrium

iii- Synthesis of progesterin receptors in endometrial tissue

b) Myometrium: estrogen increases:

- The uterine blood flow.

- The amount of contractile proteins (actin and myosin).

- Excitability and spontaneous contractility.

- Number and sensitivity of oxytocin receptors.

2. **Cervix:**

- Estrogens stimulate the secretion of excess thin alkaline mucus (the mucus is thinnest at the time of ovulation) to promote sperm transport.

- This thin mucus can be stretched into long threads between 2 glass slides. (Spirabarkiet test).

3. **Vagina:**

Estrogens stimulate:

a-Stratification and keratinization of vagina → increased resistance to infections and trauma.

b- Increased glycogen deposition → lactic acid production that kills bacteria.

4. **Fallopian Tubes: estrogen increases**

a-The motility of the tubes.

b-The activity and number of the cilia, which helps to propel the fertilized ovum towards the uterus.

5. **Breast: Estrogen stimulates:**

a- breast enlargement at puberty in girls.

b- growth of ducts, nipple and stroma.

c- deposition of fat.

d- pigmentation of the breast areola specially in the first pregnancy *period*

e- the increases of blood flow of breast.

C) Effects On Secondary Sex Characters:

1. **Hair:**

- Less body hair and more scalp hair.

- Hairline is like that of the child.

- Pubic hair is triangular with its base up i.e. flat upper border.

- Growth of pubic & axillary hair is due to adrenal androgens.

2. Skin:

- Soft & smooth. Sebaceous gland secretion is more fluid → -- inhibit acne formation.

- Excess estrogen causes dry skin and its deficiency causes greasy skin.

3. Voice:

estrogens do not stimulate the growth of vocal cords. So, female keeps the high pitched sharp voice of children.

4. Female body configuration:

Narrow shoulders, broad pelvis and characteristic fat distribution in breast, buttock and thighs.

5. Behavior effects:

Estrogen increases libido and are responsible for the psychological make up of female & sex behavior of female

D) Effects Of Estrogens on Metabolism:

1. Estrogens have protein anabolic effect on the sexual organs & bones.

2. Estrogens stimulate maturation of ossific centers, increase osteoblastic activity and union of epiphyses of bones.

plasma

3. Systemic action of estrogen:

a- VD by increasing the local production of nitric oxide.

b- Lowers the plasma cholesterol, thus inhibiting atherogenesis. However, large doses of estrogen (orally active) can promote thrombosis due to ++ hepatic production of clotting factors.

4. Estrogens have anti-insulin effect.

D) Effects On Endocrine Glands

1-Increase the size of pituitary gland.

2-Regulate gonadotropin secretion (discussed before).

2. PROGESTERONE:

Synthesis and Secretion of Progesterone: -

- Progesterone is a C₂₁ steroid secreted by the corpus luteum, placenta and in small amounts by the ovarian follicles and adrenal cortex.
- It is an important intermediate in steroid biosynthesis in all tissues that secrete steroid hormones.

The theca cells of corpus luteum provide pregnanolone to granulosa cells to synthesize progesterone.

In addition, the granulosa cells can form progesterone de novo

Transport and Metabolism of Progesterone: -

- Plasma progesterone level is 0.9 ng/ml during the follicular phase and increases 20 folds to reach a peak value of 18 ng/ml in midluteal phase. Plasma progesterone is present in 2 forms: 2 % free & 98 % bound to proteins (80 % bound to albumin and 18 % is bound to progesterone binding globulin).
- Progesterone is metabolized in the liver. It is converted to pregnanediol, which is excreted in urine.

Note:

Heat shock proteins are a group of intracellular proteins, the amount of which increases when cells are exposed to heat & stress.

Mechanism of action of progesterone:

The protein receptor of progesterone is bound to heat shock protein in absence of the steroid. Progesterone receptor binding releases this heat shock protein, leading to exposure of DNA-binding domain of the receptor.

There are 2 progesterone receptors: progesterone receptor A & progesterone receptor B.

Actions of progesterone

A) On Secondary Sex Organs:

1- Uterus: *a Antiestrogen on myometrial cells → -- excitability*

b) It controls the secretory phase of menstrual cycle.

c) It helps implantation and formation of the placenta.

d) It maintains pregnancy because:

- It prepares endometrium for implantation of the fertilized ovum. (*decidualization*)
- It inhibits uterine contractions by hyperpolarization of the endometrium.
- It decreases the myometrium sensitivity to oxytocin.

- It --- estrogen receptors in endometrium & ++ conversion of estradiol to less potent esterone.

2-Fallopian Tubes:

Progesterone stimulates secretion of mucous which is necessary for the nutrition of the fertilized ovum.

3- Vagina:

Progesterone stimulates thick secretion, epithelial proliferation with leukocytes infiltration.

4-Mammary Glands:

- a- It stimulates the development of lobules & alveoli.
- b- It induces differentiation of estrogen prepared ductal tissue.
- c- It supports the secretory function of breast during lactation.

B) Action on the ovary:

Progesterone in minute amounts in the preovulatory stage augments the LH surge.

Large oral doses of progesterone can inhibit LH secretion & hence inhibit ovulation

C) Thermogenic Action:

Progesterone is responsible for the rise in basal body temperature (0.5 C) at the time of ovulation & and throughout the second half of the cycle.

D) Respiration:

Progesterone stimulates respiration —————> decreased CO₂ tension.

E) Electrolyte Balance:

- 1- Progesterone like glucocorticoids causes Na, Cl & H₂O reabsorption from distal tubules.
- 2- In large doses, progesterone may increase Na & H₂O excretion by competing with aldosterone on its receptor

ABNORMALITIES OF OVARIAN FUNCTIONS:

1) Hypogonadism: *Prepubertal or Postpubertal*

Causes

- 1-Primary hypogonadism: congenital absence of ovaries, or ovarian disease during childhood.
- 2-Secondary hypogonadism: pituitary or hypothalamic disease.

Manifestations:

A. Prepubertal hypogonadism:

1. Primary amenorrhea and sterility.
2. Secondary sex organs remain infantile.
3. Secondary sex characters do not appear.
4. The patient is tall due to delayed epiphyseal union.

B. Postpubertal hypogonadism:

1. Secondary amenorrhea and sterility.
2. Secondary sex organs regress.
3. Secondary sex characters regress.
4. Osteoporosis and muscle wasting.

2- Ovarian Hypersecretion:

- a-Estrogen secreting ovarian tumors in childhood —————> precocious sexual development.
- b-Granulosa cell tumor of the ovary (rare) occurs after the menopause. It secretes excessive amounts of estrogens.

ABNORMALITIES OF OVARIAN CYCLE

1) ANOVULATORY CYCLES

Definition: failure of ovulation.

Causes:

- 1-Lack of enough LH.

2-Lack of ovarian follicle response to LH e.g. ovarian hypogonadism.

3- Excess Prolactin or emotional stress: $\longrightarrow$ -- GnRH release $\longrightarrow$ -- FSH and LH.

Anovulatory cycles occur:

- a) In the first few cycles following puberty.
- b) In the last several cycles prior to menopause.

Characteristics:

Failure of ovulation $\longrightarrow$ failure of corpus luteum formation $\longrightarrow$ absence of progesterone secretion which leads to:

- 1-Absence of the secretory changes in endometrium.
- 2-The cycle period is shortened

Diagnosis of ovulation:

1- Endometrial biopsy: to examine the presence of the secretory pattern of endometrium by the functioning corpus luteum (cork screw glands filled with secretion).

2- Folliculometry by sonar.

3- LH surge detection by blood hormonal assay. *4 - ++ progesterone in plasma*

5 - ++ body temp. 0.5°C in 2nd half of menstrual cycle

6 - Mittelschmerz pain i.e. lower abdom. pain. at ovulation due to peritoneal irritation

2) Amenorrhea:

a- Primary amenorrhea:

It is associated with signs of immature sexuality e.g. small breasts.

b- Secondary amenorrhea:

Cessation of cycles in females with previously normal periods.

Causes:

- i- Pregnancy (main cause).
- ii- Emotional stress.
- iii- Hypothalamic or pituitary disorders.
- iv- Primary ovarian or systemic diseases.
- v- Menopause

3) Hypomenorrhea: Scanty menstrual flow.

4) Menorrhagia: Abnormal profuse menstrual blood flow.

5) Metrorrhagia: Bleeding between regular periods.

6) Dysmenorrhea: painful period

7) Oligomenorrhea: reduced frequency of menstrual periods.

MENOPAUSE

- It means stoppage of female sexual cycle (ovarian & menstrual), with lack of female sex hormones.
- It occurs at the age of 45-50 years

Cause of menopause:

- At the age of 45 years, only a few primordial follicles are left to be stimulated by FSH and LH → -- estrogen secretion by ovary, which becomes insufficient neither to inhibit FSH and LH nor causing their ovulatory surge.
- Few years later, the remaining follicles become atretic and estrogen production falls to almost zero.

Manifestations of menopause:

- 1-Amenorrhea (loss of menstruation).
- 2-Osteoporosis due to absence of the estrogen anabolic effect on bones.
- 3-Gradual loss of 2ry sex characters.
- 4- Psychic disorders as: anxiety, irritability, depression, dyspnea.
- 5-Hot flushes.

Treatment:

- 1) Administration of small amounts of estrogen.
- 2) Intake of milk and vit. D to avoid osteoporosis.
- 3) Psychotherapy in severe psychic disorders.

CONTRACEPTION:

Definition: temporary prevention of pregnancy.

Methods of contraception:

1) Natural family planning (fertility awareness): 80-90% success

By avoidance of sexual intercourse in the expected fertile period.

It includes:

- a- Sympatothermal method: by observation of midcycle abdominal discomfort or pain, sustained rise of body temperature & thinning of cervical mucus 2 weeks after the onset of menstruation.
- b- Safe period (rhythm method): by avoiding intercourse at least 72 hours before & after the predicted time of ovulation.

After observation of menstrual cycle for 8 months, the fertile period can be calculated by:

- a- Subtracting 18 days from the shortest cycle to obtain 1st fertile day.
- b- Subtracting 11 days from the longest cycle to obtain last fertile day.

2) Hormonal suppression of ovulation (contraceptive pills):

a- Single hormone therapy:

- i- moderate to large doses of estrogen daily for 3 weeks / month → -- GnRH & inhibition of ovulation.

Side effects: abdominal bleeding, nausea or ++ danger of vaginal or cervical cancer.

ii- Synthetic progesterone pills (progestins):

Ovulation occurs, but pregnancy does not occur because:

- Endometrium is never typically secretory.
 - Cervical mucus is too thick to sperm penetration.
- N.B. Recently, implants of progestins are inserted under the skin to prevent pregnancy up to 5 years.

b- Combined hormone therapy:

Progestins combined with estrogens.

Pills are administrated for 21 days then stopped for 5-7 days then started again.

Actions:

- --- LH release.
- Alters tubal motility to discourage fertilization.
- Modifies endometrial maturation.
- Renders cervical mucus-less susceptible to sperm migration.

3) Intra-uterine devices (IUD):

Plastic or metal IUD causes changes in the duration of the sexual cycle but not alter the menstrual cycle.

Actions:

- Prevention of implantation of the fertilized ovum.
- Preventing ascent of the sperms in Fallopian tube to fertilize the ovum (spermicidal effect).
- Some IUDs slowly release progesterone or progestins.

4) Local devices:

- Vaginal jellies or creams have spermicidal affect.
- Male rubber sheaths (condoms); it is also considered prophylactic against sexually transmitted diseases.

5) Subcutaneous implants: of progestin e.g. levonorgestrel will prevent pregnancy for 5 years

6- Surgical: tubal ligation

FERTILIZATION

- It is the process of fusion of a sperm with a mature ovum to form a zygote.

Maturation of an ovum:

Shortly before ovulation, oocytes completes its 1st meiotic division at the surge of LH → the 1st polar body & a secondary oocytes with haploid number of duplicated chromosomes

Before fertilization, these secondary oocytes start its 2nd meiotic division, which became arrested in metaphase by pp39mos & is completed only when fertilization occurs

Transport of mature ovum:

- After ovulation, ovum and corona radiata (surrounding granulosa cells) is expelled in the peritoneal cavity to be picked by the fimbria of the Fallopian tube & directed to the dilated intermediate portion of the fallopian tube "the ampulla" by tubular cilia. In the ampulla, fertilization usually occurs at the 14th - 16th day of ovarian cycle.

- The released ovum retains the capacity to be fertilized for 12-24 hours. While, spermatozoa remain capable of fertilization for 1-2 days.

Sperm capacitation:

- 6-7 hours in the female genital tract before the sperms acquire the capacity to fertilize ovum.
- During this period, a change in the surface coating of spermatozoa occurs.

Factors help the ascent and protection of the sperms:

- 1- Fine uterine and Fallopian tube contractions during and after sexual intercourse.
- 2- The alkaline seminal fluid, which reduces the acidity of vaginal fluid.
- 3- Ability of the newly ejaculated semen to coagulate to prevent the leakage of sperms from vagina.
- 4- Highly viscous cervical mucus at ovulation becomes more liquefied to allow the sperms to pass through (effect of estrogen).
- 5- Suction of the sperms into the uterus by negative pressure during intercourse

Fertilization involves the following events:

a- **Chemo- attraction** of the sperm to the ovum by substances produced by the ovum.

b- **Adherence** of the sperm to the zona pellucida.

The zona pellucida is composed of 3 glycoproteins (ZP1, ZP2 & ZP3).

Receptors on the plasma membrane of the sperm cell bind to ZP3

initiating a signal transduction cascade → acrosomal reaction

c- **Penetration of sperm to zona pellucida.**

The sperm binds to a sperm receptor called ZP3 in the zona pellucida. This is followed by acrosomal reaction.

Acrosomal reaction:

It is the breakdown of acrosome (lysosome - like) organelle in the sperm head.

This leads to the release of various enzymes including (acrosein), which is a trypsin- like protease. Acrosein facilitates the penetration of the sperm through zona pellucida.

During acrosomal reaction, an increase of Ca^{++} triggers the exocytosis of acrosomal contents → penetration of sperm to zona pellicuda

d- **Adherence of sperm head to cell membrane of the ovum & break down of fusion area with release of the sperm nucleus into the ovum cytoplasm.**

One sperm reaches the ovum membrane; the fusion with the ovum membrane is mediated by specific proteins on the surfaces of the 2 cells. This fusion stimulates the formation of IP3 in the oocytes causing Ca^{++} release from internal stores.

This rise in Ca^{++} triggers the:

a) Cortical reaction:

Exocytosis of small granules which lie beneath the plasma membrane of oocytes $\rightarrow$ release of enzymes that acts on zona pellicuda glycoproteins causing them to harden. This prevents polyspermy (fertilization of ovum by more than one sperm)

b) Completion of 2nd meiotic division:

The result is an oocyte with a haploid number of unduplicated chromosomes & extruded second polar body.

The 1st & 2nd polar bodies lie close beneath the zona pellucida

Functions of zona pellicuda:

1- It contains glycoprotein ZP 3 that interacts with sperm receptors & facilitates penetration

2- Cortical reaction on zona pellicuda surface to prevent polyspermy

3- It Keeps early dividing cells of the zygote (blastomere cells) together until implantation.

- The sperm penetration of cumulus oophorus is mediated by:

1-Acrosein: proteinase enzyme.

2- Hyaluronidase.

Both enzymes are present in the inner acrosomal membrane of the sperm head.

3- Ca^{++} influx:

- Once the sperm reaches the ovum, microvilli from ovum protrude (fertilization cone) - and engulfs the sperm head in the ovum cytoplasm. Then the 2nd

meiotic division of the ovum is completed within 2-3 hours.

- The unpaired 23 chromosomes in the ovum (maternal gamete) combine with the 23 chromosomes of the sperm (paternal gamete) to produce the zygote, with the diploid chromosomal number.

Fetal graft:

The rejection of the fetus is prevented by:

1- **Expression of HLA- G** (non- polymorph- gene) by placental trophoblast rather than expressing MHC class I, II. This prevents development of antibodies against fetal proteins.

2- **FAS- ligand** exists on the surface of the placenta. This binds to T- cells causing them to undergo apoptosis.

3- **Decrease in the circulating antibodies in the mother.**

4- Immunosuppressive agents secreted by blastocyst e.g. HCG

Initial Development of embryo:

- After the zygote is produced, cleavage (simple mitotic divisions) begins, while it is still within the zona pellucida.
- During cleavage, the zygote cells divide but the total cell mass remains unchanged, and hence with each successive division, the cell size gets smaller.
- During cleavage, the zygote descends down in the Fallopian tube towards the uterus aided by the ciliated epithelium of the Fallopian tube (3-5 days).
- Nutrition of the zygote during its transport through the Fallopian tube is supplied by the large amounts of Fallopian tube secretion.
- Morula (50-100 cells) is implanted in the uterine endometrium. This takes place 2-4 days after the developing zygote reaches the uterus. During this period, the developing zygote obtains its nutrition from the endometrium secretions, which is rich in proteins, glycogen, lipids and even some minerals.

Non- dysjunction:

It is a defect in the gametogenesis in which a pair of chromosomes fails to separate so that both go to one of the daughter cells during meiosis.

Turner syndrome:

- It is one of the 4 abnormal zygotes resulting from non- dysjunction to one of the X chromosomes.
- Female's zygotes in this syndrome are individuals with XO chromosomal pattern.
- They suffer from:
 - 1) Rudimentary or absent gonads (but with development of female external genitalia)
 - 2) Short stature
 - 3) No maturation after puberty
 - 4) Congenital abnormalities.

Klienfelter's syndrome:

- The male individuals of this syndrome have XXY chromosomal pattern.
- This resulted from non- dysjunction & fertilization of the daughter cell possessing the XX chromosomes by a sperm with a Y chromosome.
- These individuals have:
 - 1) Normal male genitalia
 - 2) High testosterone secretion at puberty for development of male characteristics
 - 3) Abnormal seminiferous tubules
 - 4) Higher incidence of mental retardation

Premplantation

Blastocyst stage:

A fluid filled cavity forms within the mass of morula cells separating the cells into:

- a) The inner cell mass is known as embryonic proper. It forms the embryonic tissues
- b) The outer cell mass is the trophoblasts

The zona pellicuda prevents the zygote cells from falling apart in next shed.

The shedding is due to lytic factors released from the decidual cells mainly plasmin.

If the cells divide into 2 separate groups, identical twins result

Pinopodes:

- They are small finger- like protrusions that arise on endometrial cells between day 19 & day 21 of ovarian cycle (at time of implantation) & persist for 2- 3 days to determine the degree of implantation.
- They are progesterone dependent & inhibited by estrogen
- Pinopodes endocytose macromolecules & uterine fluid present in the uterine lumen allowing the embryo & uterine epithelium to approximate one another more closely.

Implantation:

- It is the process of the embedding of the blastocyst into the uterine epithelium (endometrium).
- It occurs on the 6th – 8th days after ovulation
- It occurs in 3 steps:

1) Apposition:

- It is early loose connection of the blastocyst with endometrial epithelium.
- It usually occurs at the site of rupture of the zona pellicuda where it is possible for the cell membranes of the trophoblast to make direct contact with the cell membranes of the endometrium.

2) Adhesion:

- It occurs between microvilli arising from the trophoblasts & the uterine epithelium.
- It involves ligand- receptor interactions. The receptors are members of the integrin family.
- They can be either on the blastocyst or on the endometrium.
- Integrins are bifunctional integral membrane proteins:
 - a) On their intracellular side, they interact with cytoskeleton.
 - b) On their extracellular side they have receptors for matrix proteins such as collagen, laminin & fibronectin

3) Invasion:

- The trophoblast attaches to the endometrium & rapidly proliferates into:

a) Inner cytotrophoblast

b) Outer syncytiotrophoblast

- Long protrusions from the syncytiotrophoblast extend between the uterine epithelial cells.

- These protrusions dissociate the endometrial cells & penetrate the basal lamina by secreting:

a) Autocrine factors

b) Proteases that degrade extra- cellular proteins

c) Tumor necrotic factor alpha which interferes with the expression of cell adhesion molecules

- HCG acts as autocrine growth factor thus promoting trophoblast growth & placental development

HCG also has protease activity that helps in the process of adhesion.

This enables the blastocyst eventually to:

a) be buried eventually in the endometrium

b) Feed on the fluid & nutrients released from endometrial cells.

- The stroma cells of endometrium, under the effect of the progesterone are changed into swollen cells known as decidua cells

- For 8- 12 weeks after implantation, most of the nutrients obtained by the embryo are from the digestion of the decidua by trophoblasts

Continuation of pregnancy:

- The secretion of HCG (human chorionic gonadotrophin) by trophoblasts continues for 60 days to maintain the corpus luteum after which placenta is able to take over the role of the C.L.

- Importance of C.L. in early pregnancy is secretion of estrogens and progesterone to:

1-Inhibit release of pituitary gonadotropins, to prevent the growth of ovarian follicles.

2-Promote the growth of the uterus and mammary glands.

DEVELOPMENT OF THE PLACENTA

- The outer most layer of the fertilized ovum, or zygote is the trophoblast (chorion) which serves for nutrition and protection.

The syncytiotrophoblast starts to proliferate rapidly forming pseudopodia like masses.

These masses soon develop into finger- like processes (trophoblastic cords), which attach deeper to the endometrium.

a) Some cytotrophoblast proliferate & invade the syncytiotrophoblast forming primary chorionic villi

b) Invasion of mesenchymal cells in primary villi changes it to secondary villi

c) Formation of fetal capillaries & amplification of surface area of villi results in development of tertiary villi

Note:

Continued differentiation & amplification of surface area of villi produce chorionic villi at 14th – 16th day after fertilization

- Around the chorionic villi, blood sinuses from the mother develop. These sinuses are filled with blood coming from the uterine arteries, before draining into the uterine veins.

N.B. fetal and maternal are separated by the trophoblastic layers forming the fetal membranes (placental barrier).

The membranes which form the placental barrier, include:

- 1-Outer syncytial trophoblast.
- 2-Middle mesenchymal layer, which grows under syncytial trophoblast.
- 3-Inner cytotrophoblast.
- 4-Wall of fetal capillaries.

PLACENTA

- The placenta is a circular disc. With a diameter of 20 cm and a thickness of 3.5 cm at full maturity.

- It usually weighs 500 grams.

- The embryo is joined to the placenta by the umbilical cord, which contains 2 fetal (umbilical) arteries and a vein, which connect to fetal capillaries in the placental villi.

- During the early months of pregnancy, the placental permeability is relatively low, due to:

1. Small surface area of placental membranes.
2. Placental villi have relatively thick layers in early pregnancy.

• As the placenta gets older, its permeability progressively increases until the last month of pregnancy then towards the end of pregnancy, the placental permeability decreases, due to decrease of placental efficiency by age.

Circulation in the placenta:

- Deoxygenated fetal blood enters the umbilical cord via the 2 umbilical arteries then to the fetal capillaries of chorionic villi.

- The exchange of nutrients, gases and other substances takes place between the fetal capillaries in chorionic villi and the maternal sinuses, which are filled with blood coming from uterine arteries.

- **This exchange is aided by:**

1. Reduction of the blood pressure in the maternal sinuses.
2. Sluggish blood flow in maternal sinuses.

The sluggish circulation in the maternal sinuses of the placenta is due to:

- 1- Small blood lakes which arise near the chorion plate which --- the force of the arterial spurts & reduce blood velocity.
 - 2- Lateral spreading of the blood & its reversal in direction
 - 3- Geometry of the maternal blood vessels:
 - a) Perpendicular spiral arterioles
 - b) Parallel venules to the chorion plate
 - 4- Uterine contractions occur during pregnancy which leads to:
 - a) Weak arterial inflow
 - b) No venous drainage
- a & b increase blood flow in the intervillous spaces (maternal sinuses)

- **Maternal- placental- fetal unit:**

The placenta by itself can not synthesize the sex steroid hormones (estrogens & progesterone)

- 1- The maternal blood supplies the placenta with cholesterol & LDL particles to form sex hormones
 - 2- The fetal adrenals & liver provide the placenta with the key enzymes (16 α & 17 α hydroxylase and 17 & 20 desmolase) to form estrogen.
- Placental sex hormones pass to maternal blood

- The blood of fetal capillaries after exchange is returned back to the fetus through the umbilical vein in the umbilical cord.

PLACENTAL FUNCTIONS

1- Diffusion of gases:

A) Diffusion of O₂:

- PO₂ in the mother's blood is 50-60 mmHg, while the PO₂ in fetal blood is 20-30 mmHg $\longrightarrow$ O₂ diffusion through the villi from maternal blood to fetal blood.
- *Most of the O₂, transported by fetal Hb is taken by tissues due to:*

- 1- Fetal Hb is capable of carrying 20% - 30% more O₂ than mother's Hb.
- 2- High concentrations of fetal Hb in fetus, which is 50% greater than that in maternal blood.
- 3- Bohr effect:
 - large amounts of CO₂ from fetus is diffused to maternal blood. This makes the fetal blood more alkaline, while the maternal blood becomes acidic. This allows more O₂ to diffuse to the fetal blood and increases its Hb combining capacity to O₂.
- 4- High cardiac output relative to fetal weight

B) Diffusion of CO₂:

- PCO₂ in fetal blood is 2 - 3 mmHg higher than that of maternal blood. This is sufficient for CO₂ diffusion since the solubility of CO₂ is 20 times more rapid than that of O₂.
- Moreover, the PCO₂ in maternal blood is lower than its normal value due to increase ventilatory by estrogens and progesterone during pregnancy.

2- Diffusion of nutrients:

A) Carbohydrates: -

- The glucose is diffused through the placenta by facilitated diffusion.
- The placenta can store glycogen.
- By the action of glycolytic enzymes secreted by placenta, it can convert this glycogen to glucose.

B) Fats: -

Diffuse readily but more slowly than glucose.

C) Minerals and Vitamins:

- Na⁺, K⁺, Cl⁻ are transferred to fetus by simple diffusion.
- Ca⁺⁺, Ph⁻, Fe⁺ are transferred by active transport.
- Water-soluble vitamins as vitamins B and C are present in high concentrations.

3- Diffusion of Fetal Excretory Products:

- These include urea, uric acid, creatinine (non protein nitrogen's).

4- Protective Function of placenta:

- The placenta acts as a barrier against invasion of harmful substances to fetus. Thus, the first three months of pregnancy before placental development is the period for congenital defects to occur since the fetus is most sensitive to damage by viruses or drugs.
- Placenta can permit passage of IgG but not IgM which give passive immunity.
- Placenta can permit passage of some harmful materials such as most drugs, viruses and Rh - agglutinin → fatal death or severe malformations.

5- Endocrinal Role of placenta:

The placenta can act as an endocrinal organ and secrete the following hormones:

A. Human chorionic Gonadotropin (HCG):

- Syncytial trophoblast cells into the fluids of the mother secrete Human chorionic Gonadotropin (HCG), shortly after implantation.
- It can be detected by radio-immunoassay & measured in blood as early as 6 days and as early as 14 days in urine after conception.
- It is formed of α and β subunits. The α - subunit is similar to that of LH, FSH & TSH.
- It is a glycoprotein with the same function of luteinizing hormone (LH), but HCG is not inhibited as LH by the high levels of progesterone and estrogens.
- It increases rapidly to reach its maximum level 7 - 9 weeks of pregnancy.

Functions:

- 1- It prevents degeneration of the corpus luteum, which maintains pregnancy by its secretion of estrogens and progesterone.
- 2- It exerts an interstitial cells stimulating effect on testes in male fetus leading to secretion of testosterone.
- 3- it increases growth of endometrium and storage of more nutrients in decidual cells.
- 4- HCG acts as immunosuppressive agent to prevent fetal rejection.
It also promotes implantation & helps growth of trophoblasts & placental development.

B. Estrogens:

The secretion of estrogens by placenta syncytial trophoblasts is characterized by:

- 1) Most of the estrogens is estriol.
- 2) They are not synthesized denovo i.e. they are derived from "dehydroandrosterone", which is converted to estradiol, estrone and estriol.

Functions of Estrogens in Pregnancy:

- 1) Growth of uterus.
- 2) Growth and enlargement of mammary glands.
- 3) Relaxation of pelvic ligaments, which helps the easy passage of fetus through birth canal.
- 4) Increase number & sensitivity of oxytocin receptors in uterus.

C. Progesterone:

It is secreted by syncytial trophoblast.

Functions of Progesterone:

- 1) Development of decidual cells needed for fetal nutrition.
- 2) Decreases uterine contractility during pregnancy.
- 3) Increases secretions of Fallopian tube and endometrium before implantation to provide the necessary nutrition for the zygote development.
- 4) Prepares breast for lactation by increasing growth of breast alveoli.

D. Human chorionic Somatomammotropin (HCS) = human placental lactogen (hPL) = chorionic growth hormone prolactin (CGP):

- It is a protein hormone secreted by placenta at 5th week of pregnancy.
- It is a lactogenic & has small amount of GH activity.
- Since it is similar in structures to GH, thus may explain the unincreased amount of GH secreted from natural pituitary gland. Thus, it may function as maternal GH of pregnancy.
- It has the following effects:
 - a) Partial development of breast.
 - b) Deposition of protein in tissues.
 - c) Provides great amount of glucose from mother to the fetus by:
 - 1- Decreasing insulin sensitivity and glucose utilization by mother.
 - 2- Increasing release of fatty acids from fat stores to provide mother with an alternative source of energy.

Other Hormonal secretions during pregnancy:

A) OTHER HORMONAL SECRETIONS BY PLACENTA

1. RELAXIN:

It is a polypeptide hormone secreted by placenta.

Functions:

- a- Relaxation of the pubic symphysis & other pelvic joints.
- b- It softens & dilates the uterine cervix, thus facilitates labor.
- c- It inhibits uterine contractions.
- d- It may play a role in the development of mammary glands.

N.B. in males, it is secreted by the prostate gland & found in the semen. It may help to maintain sperm motility & sperm penetration of the ovum.

2- CORTICOTROPIN RELEASING HORMONE:

- It increases the secretion of dihydro- androstenedione by direct action on the fetal adrenal thus, increasing the circulating estrogen.
- It increases secretion of ACTH & therefore cortisol.

3- β endorphin.

4- α MSH.

5- Inhibin & GnRH:

GnRH stimulates HCG, while inhibin inhibits HCG secretion in a paracrine manner

6- Leptin.

7- Prolactin.

8- Free HCG α subunits. The function of these subunits is suggested to stimulate the endometrial (local) prolactin secretion.

9- Prorenin.

B) PITUITARY HORMONES:

The anterior pituitary gland of the mother is stimulated by placental hormones to secrete increased amounts of:

- a) Corticotropin.
- b) Thyrotropin.
- c) Prolactin.

While FSH & LH are greatly suppressed.

C) Other glands:

- Pancreas $\longrightarrow$ ++insulin
- Thyroid gland $\longrightarrow$ ++ thyroid hormones.
- Parathyroid gland $\longrightarrow$ to maintain normal Ca^{++} conc. in maternal blood to compensate for Ca^{++} given to baby
- Cortical secretions $\longrightarrow$ ++ glucocorticoids & ++ Aldosterone.

PREGNANCY TESTS

They depend on testing the presence of HCG in urine or blood:

These tests include:

A. Immunological (Agglutination) tests:

These tests are rapid and specific.

1) The urine is added to HCG antibodies in the presence of sensitized RBCs or latex particles coated by HCG.

- If woman is pregnant: The urine containing HCG will combine with HCG antibodies —→ no agglutination of latex particles or RBCs will occur.

- If woman is not pregnant: —→ agglutination occurs.

This method is known as inhibition of coagulation.

2) Direct coagulation:

The latex particles coated with anti – HCG react with the urine of the patient.

If coagulation occurs, woman is pregnant.

B. Radioimmunoassay:

Used for the polypeptide β - subunit receptor of HCG.

PARTURITION (LABOR)

- It is the process of expulsion of the fetus, the surrounding membranes and the placenta from the uterus.

- It requires strong coordinated uterine contractions aided by voluntary abdominal muscles contractions.

- The exact mechanisms which initiate labor are not exactly clear, but it involves a combination of these factors:

1) Hormonal factors:

a) Ratio of estrogen /progesterone during pregnancy:

- Progesterone inhibits uterine contractions thus it prevents expulsion of fetus.
- Estrogen has the tendency to stimulate uterine contractions

The two hormones are secreted in increasing amounts throughout pregnancy until the 7th month after which:

- Progesterone levels remains constant or slightly decrease.
- Estrogen secretion continues to increase.
- Ratio of E / P increases to increase uterine contractility.

b) Oxytocin:

Increased levels of fetal oxytocin are believed to initiate labor, while maternal oxytocin maintains uterine contractions during labor.

- Oxytocin stimulates:

- 1- prostaglandin secretion from decidua.
- 2- strong uterine contractions.

N.B.

High levels of estrogen at the end of pregnancy increase the synthesis & sensitivity of oxytocin receptors.

c) Fetal- hypothalamic- pituitary axis:

It stimulates uterine contractions.

d) Prostaglandins:

* It is secreted from: decidua & fetal membranes.

Actions:

- 1-Direct stimulation of uterine contractions.
- 2-Induce the action of oxytocin on uterine muscle.
- 3- Softens, dilates & thins out the cervix during early labor with invasion of leucocytes.

2- Mechanical Factors:

- Stretch of uterine muscles induces uterine contractions.
- Stretching or irritation of cervix stimulates reflex uterine contractions.
- Positive Feedback theory of labor:

This theory suggests that once the uterine contractions become greater than a critical level, there is a positive feedback, which initiates a vicious circle of even stronger contractions.

It depends on:

- 1) Cervical stretch (by descent of baby's head in the cervix) stimulates reflex contractions in the fundus and body of uterus, which become progressively stronger, with more cervical stretch and dilatation.
- 2) Cervical stretch and dilatation also stimulates posterior pituitary gland to secrete oxytocin, which increases the uterine contractility (*Fergusson reflex*)

Stages of labor:

- 1-First stage;** involves the stretching of cervix and initiation of uterine contractions.
- 2-Second stage;** involves the expulsion of the baby from the birth canal.
- 3-Third stage;** involves the expulsion of fetal membranes and placenta after separation from its implantation site.

LACTATION

Development of the breast begins at puberty by the action of ~~estrogens~~ and progesterone.

During pregnancy:

A. Increased estrogens levels causes:

- Growth of ductal system.
- Increased stroma.
- Increased fat deposition.

These estrogen effects on the breast are aided by:

- Prolactin
- Growth hormone.
- Adrenal glucocorticoids.
- Insulin.

B. Increased progesterone levels

With the aid of the fore - mentioned hormones, progesterone cause:-

- Growth of breast lobules.
- Growth of alveoli.
- Development of secretory characteristics in alveolar cells.

Secretion of milk:

A) Hormones:

1) Prolactin promotes milk secretion.

It is secreted in the mother from 5TH week of pregnancy until birth.

The main stimulant after birth is suckling.

2) Human chorionic somatomammotropin:

Secreted by placenta & has also lactogenic properties.

It is promoted at 2nd - 3rd week after labor. It requires adequate amounts of:

- Parathyroid hormone.
- Cortisol.
- Growth hormone.

These hormones provide the elements necessary for milk synthesis as fatty acids, amino acids, glucose and calcium.

B) Suckling maintains & augments milk secretion by prolactin secretion.